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FACILITATION AND DIFFICILITATION EFFECTED BY NERVE IMPULSES IN PERIPHERAL FIBERS

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(Received for publication August 4, 1939)

SUMMATION and inhibition of impulses in the nervous system must occur at points where they are transferred from one responding unit to another, since an impulse initiated in any part of a normal neuron inevitably traverses the whole of it. Therefore, in attempting to ascertain whether these reactions can occur in nerve fibers an artificial synapse or physiological discontinuity must be provided. Such a synaptic relation cannot be effected by the approximation of two medullated fibers since it has not been possible to demonstrate a measurable effect on one medullated fiber of activity in a contiguous fiber (Blair and Erlanger, 1932), though this does seem to be possible in the case of nonmedullated fibers (Jasper and Monnier, 1938). Neither can a valid artificial synapse be made by damaging a fiber locally since, as is well known, any disruption of the fiber's structure lowers its electrical resistance locally and so reduces the number of current lines eddying ahead from active fiber across the damaged locus, to the fiber to be activated beyond.

In anode polarization, however, one has a means of producing at a node of Ranvier a local discontinuity without changing the structure or lowering the local ohmic resistance of the fiber and thus can interpolate an artificial discontinuity which presumably resembles the natural synapse in some of its electrical aspects, at least. Through the use of this method it has been possible to demonstrate the transmission of a nerve impulse across a nonresponding gap in a fiber (Blair and Erlanger, 1939), the temporal summation of two nerve impulses (Blair and Erlanger, 1936), and that (Erlanger, 1939) such summation has the temporal characteristics of the summation of two nerve impulses at the neuromuscular junction, as described by Bremer and Homès (1930). Moreover, casual reference has been made to observations on the temporal summation (facilitation) by multiple impulses in such a preparation (Erlanger, 1939).

The present paper concerns itself with the latter set of observations, which includes an attempt to determine the magnitude of facilitation as affected by the number and by the spacing of the blocked spikes. It deals also with the consideration of a process, designated difficilitation,* characterized by an increase in the degree of block, and elicitable by a conditioning tetanus followed by a pause. In addition, evidence, not yet conclusive, will be presented indicating that the action potentials so blocked may be directly responsible for the continuance of this state of difficilitation. Such difficilitation then would be comparable with inhibition.

* Substantive coined from difficilitate, the antonym of facilitate.

METHODS

Action potentials of single nerve fibers of the phalangeal preparation of *Rana pipiens* have been observed or recorded with the electron oscillograph by techniques previously described (Blair and Erlanger, 1933; Erlanger and Blair, 1934). The stimulating electrodes are on the central end of the preparation. The anode of a polarizing circuit is connected with the proximal lead electrode and the cathode rests on the nerve a few millimeters central to it, both on the peripheral end of the preparation. The voltage needed to produce at the anode a conduction discontinuity of the desired grade is read on a voltage divider. In long-continued experiments block sometimes develops at the cathode; it can be recognized readily by the failure of that fraction of the conducted action potential to appear in the record seen when the block is at the lead (the anode). The polarizing electrodes are calomel half-cells; all other electrodes are of silver.

The stimuli consisted of trains of shocks delivered through the device diagrammed in Fig. 1. From it could be obtained (i) single trains consisting of any desired number of shocks at any rate and strength, and (ii) two such trains spaced by any desired interval. When the rotor-operated keys were employed the longest cycle available had a duration of about two seconds. For long tetani or wide spacings between them the rotor was disconnected and the bursts controlled manually, but the manual method could be used satisfactorily only when the experiment did not require accurate control of the timing of the bursts or of the intervals between them. The amplifier was of the capacity-coupled type; therefore slow alterations in the level of the fluorescent spot sometimes seen in the records are without significance; some of them were extraneous in origin.

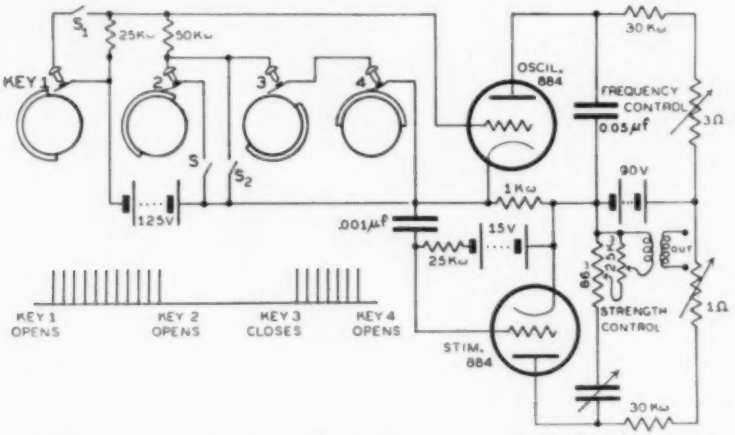

FIG. 1. Diagram of variable frequency stimulator delivering two bursts separated by a variable interval. Simultaneous opening of S_1 and closing of S_2 (D.P.D.T. switch) permits of manual control of stimulation through the master switch, S. The lower diagram shows what operation of the keys accomplishes, the verticals here representing stimuli. The rotating discs are a part of the rotor for synchronizing sweeps and stimulations. $K\omega = 1000$ ohms. $\Omega = 1$ megohm.

The preparations were stored in Ringer solution at 5°C. and, when mounted for study, were dripped with Ringer solution at room temperature. The Ringer solution was made according to the formula given by Bayliss (1920). Its pH was 8.04.* Some nerves failed to exhibit the phenomena under investigation; then it usually was possible to elicit them by increasing to three times that specified by Bayliss the calcium content of the solution applied to the phalangeal end of the preparation.

In this series of experiments much more difficulty than heretofore was experienced in limiting the response at the lead to that of a single fiber, due to the fact that a stimulus which, when applied singly, just reaches the threshold of the fiber of outstanding excita-

* Determined by Dr. H. B. Peugnet.

bility, is apt when rapidly repeated, to attain by temporal summation the threshold of other of the less irritable fibers extending the length of the preparation, an effect Gasser (1938) has compared with recruitment. However, we have through the months succeeded in making many preparations in which but one fiber has conducted to the lead throughout a set of tests. But when the responses of not more than two or three fibers are brought into evidence by recruitment, and their spikes are distinguishable by differences in configuration such as are determined by differences in height or diphasicity, it still may be possible to interpret the pictures in terms of facilitation or of difficilitation, as will become evident.

Results

Facilitation. Some conditions affecting the measurement of facilitation. As a measure of the transmissibility of nerve impulses across an anode block we have used the degree of polarization required to maintain the block. The polarizing current is adjusted by means of the voltage divider so that it *just* suffices to block the desired number of the impulses of a tetanus, the first, for example, the first two only, and so on. Since the excitability of a fiber is constantly fluctuating (Blair and Erlanger, 1933) the intensity of current that just suffices to block a given number of the spikes of a burst must be defined as the one that blocks that number in 50 per cent of a sufficient number of trials. Rarely will fewer than 12 trials (sweeps) suffice for a determination; usually many more are needed. Since the sweep cycles have occupied about 2 seconds and since in many of the experiments it has been necessary to make scores of determinations of blocking thresholds, the anode polarization often, indeed usually, had to be long continued, and therefore it became necessary to know how a block determined by anode polarization changes with time.

The results of an experiment planned with this in mind are collected in Fig. 2. One spike per sweep (1.82 sec.) was made to course along the fiber and the voltage needed to block these impulses was followed. The preparation had not previously been polarized but, when started, the polarization was maintained continuously although with each determination the voltage was adjusted to just blocking intensity. Every determination made during a 57 minute period is included in the graph. The polarizing voltage then was kept at the 57 minute level for a period of unnoted duration before starting an experiment to be described below. It is seen that the voltage needed to maintain a block diminishes with the time,* but that eventually the curve begins to run almost horizontally. One way of minimizing the changing effectiveness of the anode as a block, therefore, is to apply the polarizing current but postpone the experiment proper pending the attainment of this relatively steady state.

But, as will be seen, there is in the experiments as we have had to perform them another factor influencing the voltage needed to block, a factor

* It is stated (Schafer's *Text-book of physiology*, vol. 2, p. 498) that during the period of current flow the excitability at the anode, as tested by induction shocks, falls gradually to a minimum from which it then rises slightly. Recent determinations by Schmitz and Schaefer (1933) indicate that the change at the anode reaches equilibrium in about 0.5 sec. Our times are of a wholly different order of magnitude.

that is affected by time also, namely, the period of subnormal excitability following a tetanus. This, according to Gasser (1935), may last many minutes, whereas the longest interval permitted by our rotor was about 2 seconds. The briefer the tetanus the briefer and the less significant is the subnormality. To minimize this source of difficulty one might resort to very brief tetani and this has been done where possible. But it will be seen that even when the bursts consist of fewer than 15 rapidly repeated spikes the complication may not be eliminated; and 15 spikes do not suffice to carry facilitation to the maximum attainable. The best method would have been

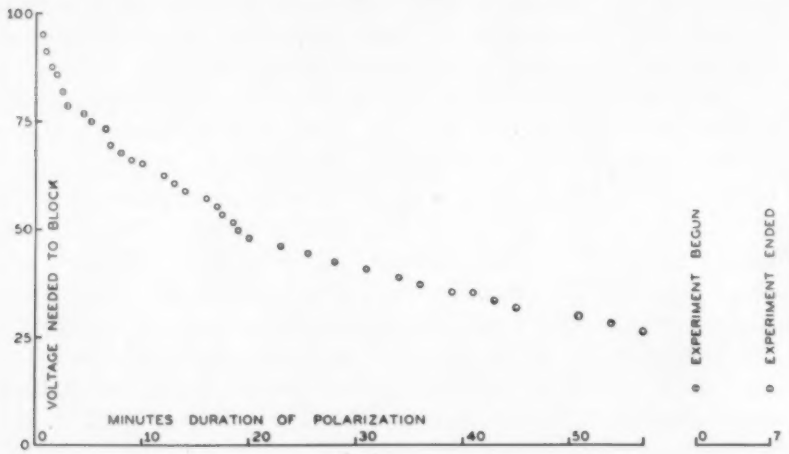

FIG. 2. Graph of the voltage needed to block one spike per sweep (*i.e.*, one stimulus per 1.82 sec.), against the duration of the polarization. The initial current strength is assigned a value of 100. After an indeterminate interval (indicated by the break in the base line) during which the polarizing circuit remained closed, the experiment plotted in Fig. 3 was begun without interrupting the polarizing circuit; it occupied the time indicated here (0 to 7). During that experiment the current needed to block the one spike per sweep fell insignificantly.

to have used rest intervals exceeding the after-potential in duration through the employment of the hand-operated switches. To have done so, however, in experiments that required scores of determinations of the threshold polarizing voltage, would have increased enormously the risk of protracting them beyond the limits of constancy of the preparation. Indeed, as it was, not a few observations had to be terminated before completion, many of them owing to the ultimate onset of block at the polarizing cathode.

That there is some factor (undoubtedly the subnormal period) in addition to the anode polarization affecting determinations repeated every 2 sec. is indicated by the continuation of the experiment just described. Present observations were begun after the polarizing current had been flowing for considerably over an hour, and at a time when its effectiveness as measured by the voltage needed to block but the one spike per sweep had reached a more or less steady state (see Fig. 2). Tetani were employed now instead

of single shocks. Each tetanus consisted of 40 spikes at the rate of 120 per sec., the interval between sweeps remaining 1.82 sec. The quiescent intervals, therefore, had a duration of 1.49 sec. All of the first 59 of this series of sweeps were recorded excepting the first two and the data included in the graph, Fig. 3, are derived from the records. The progressive increase seen here in the number of spikes required for facilitation is very much more rapid than has usually been the case; possibly this is referable to the long period of anode polarization which had preceded (and was continuing through) this observation.* At first this increase in block proceeds fairly regularly with the time, but beyond about the 15th sweep the fluctuations

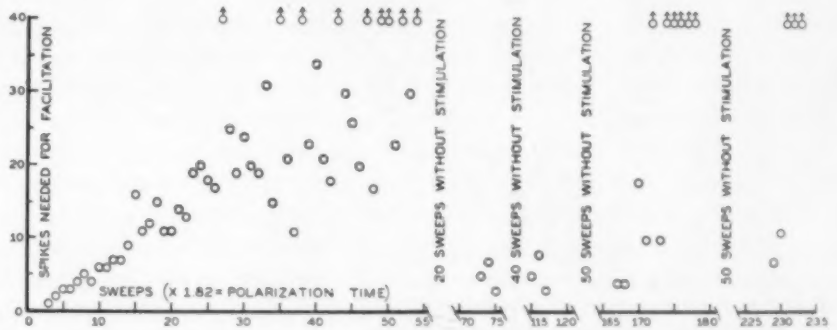
SPIKES NEEDED FOR FACILITATION
SWEEPS (X 1.82 = POLARIZATION TIME)
20 SWEEPS WITHOUT STIMULATION
40 SWEEPS WITHOUT STIMULATION
50 SWEEPS WITHOUT STIMULATION
50 SWEEPS WITHOUT STIMULATION

FIG. 3. Graph of the number of spikes required to effect conduction by facilitation, as affected by the time elapsing after establishing an anode block that just suffices at the outset to block the first spike only. The polarizing voltage remains constant throughout the experiment. With each sweep, excepting where otherwise indicated, the fiber is stimulated 40 times (at the rate of 120 per sec.). The circles attached to arrows signify that the 40 spikes of the sweep did not suffice to establish conduction through the block. After the last (the 233rd) sweep polarization was stopped and the block disappeared instanter.

in the number of blocked spikes from sweep to sweep becomes considerable. With the 27th tetanus the 40 spikes for the first time cease to suffice to facilitate to the conduction level, and then this situation recurs with increasing frequency as the experiment proceeds. The significance of this increasing fluctuation in the number of spikes blocked will be considered later.

At the moment we are concerned with the cause of the rapid and progressive increase in the number of spikes needed to overcome the block. Growing effectiveness of the anode of the polarizing circuit, at least as a potent factor, can be excluded on two counts. In the first place, the current needed to block one spike per sweep was the same at the end as at the start of this series of observations. Secondly, four times during the course of the experiment stimulation was stopped temporarily, for 20 sweeps, 40 sweeps, 50 and 50 sweeps, respectively, as indicated in Fig. 3, *but the polarization*

* In many experiments this "spontaneous" growth in the intensity of the block was so gradual that it was easily possible to determine satisfactorily the threshold blocking voltage at each level of block as it was changed experimentally.

was continued. Each period of rest immediately reduced the number of blocked spikes required to reestablish conduction—the performance became almost, though not quite, as good as it had been at the start of the experiment. But with the resumption of periodic tetanization, the anode polarization still continuing, the fiber very quickly lost again the ability to conduct. Now these fibers do not fatigue readily at the rates of stimulation employed here; therefore it becomes necessary to refer the rapid increase in the number of blocked spikes required for the reestablishment of conduction to some other cumulative factor, and this unquestionably is accumulating subnormality of excitability on the part of the postfiber.* But before discussing the influence of subnormality on these determinations an experiment on facilitation will be described in which it so happened that little or no correction was necessary for changes occurring with time.

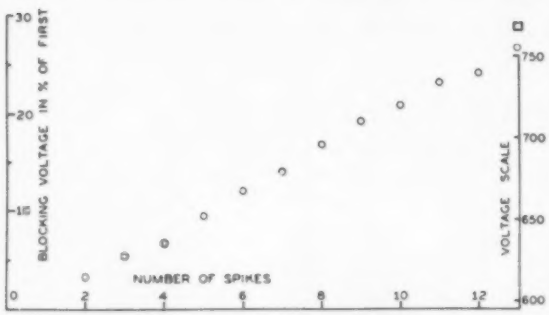

FIG. 4. Graph of the facilitation effected by blocked spikes, in relation to the number blocked. Stimulation was at the rate of 167 per sec., and therefore the intervals between circles are 0.6 msec. Ordinates (left), blocking voltage in per cent of the voltage required to block the first spike at the start of the experiment; (right), in scale divisions of the voltage divider. Abscissae, the number of spikes blocked. The ordinate for the square is the blocking voltage in per cent of the voltage required to block the first spike at the end of the experiment.

Experiments on the effect of the number of spikes and of their rate, on the amount of facilitation obtainable. In Fig. 4 are plotted the results of an experiment in which the fiber was stimulated 13 times with shocks spaced at 6 msec., the bursts being repeated about 30 times per min.† The voltage (readings on the voltage divider) sufficing for anode block of the first spike of a tetanus was 595 at the start of the experiment and 585 at the end. In other words there was relatively little change in the effectiveness of the polarizing current during the course of the experiment. Moreover, it was possible in this case so to adjust the polarizing voltage as to have conduction accomplished by any desired number of blocked spikes, regularly 1, 2 or 3, up to the limit of 13, and for considerable periods of time. The figure shows that the 13 spikes succeed in overcoming a block that exceeds by about 28 per cent the current needed to block the first spike; and though the curve is beginning to flatten, it is obvious that by no means had the maximum facilitation yet been attained.

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* It will be convenient and appropriate to designate as prefiber and postfiber the parts of the fiber proximal and distal, respectively, to the block.

† This is the observation on temporal summation of multiple spikes that is referred to in a previous publication (Erlanger, 1939).

But in most of the experiments the apparent effectiveness of the polarizing current has constantly increased; and the preliminary experiment, it will be recalled, indicates that a part of this effect is referable to the overlapping of a tetanus and of the period of subnormality following in the wake of a preceding tetanus, an overlapping which could not be avoided, owing to limitations imposed by the machinery that had to be used in order to expedite determinations.

Let us now consider a specific experiment (see Fig. 5A and B) and indicate how these factors might be expected to affect the results obtained. To repeat, the threshold blocking voltage was determined for each successive change in the number of spikes blocked, and each of these determinations was immediately followed by a determination of the current strength needed to block the first spike of the tetanus. Other conditions here were (a) cycles recurring every 1.82 sec., (b) tetani consisting of 40 spikes, (c) at the three stimulation rates, which were 100, 50 and 200 per sec. in three successive series of tests, respectively, (d) tetani which lasted, therefore, 0.4, 0.8 and 0.2 sec. and (e) fell into whatever phase of the excitability cycle after-potentials that may have obtained 1.42, 1.02 and 1.62 sec. later, respectively. Under these conditions the tetani must all have begun during the subnormal phase of the postfiber; and though there is no exact information available on the basis of which one can estimate the degree of subnormality that actually obtained, one can assume from what is known, that in general the subnormality was greater the shorter the interval between these successive tetani. Therefore, with any given rate of impulses, the larger the number of impulses blocked the less would be the subnormality developing in the postfiber; and when all of the spikes are blocked there would be no subnormality in the postfiber.

In these experiments the effects of subnormality and of anode potential *appear* to sum. Thus when but one spike of a series is blocked, and subnormality in the postfiber is high due to the long tetanization periods, relatively weak anode polarization suffices to block. As more and more of the spikes are blocked by anode polarization, and the subnormality in the postfiber consequently becomes less, relatively more anode potential is needed to maintain the block.* Now when the voltage required to block, say, 20 spikes of these bursts of 40 repeated every 1.82 sec. is being compared with that required to block only the first spike of such a burst, the subnormality eventually developing in the postfiber under the first set of conditions would be less than that developing under the second. And it is obvious that the greater the degree of block, and possibly the slower the rate of stimulation, the number of the spikes remaining the same, the larger would be the error when the voltage that blocks the first spike is employed as a yardstick. This analysis, it will be seen, is borne out in general by the experimental data.

* Since subnormality and electropositivity are associated manifestations of a fiber, it is quite possible that this positivity does enhance the depressing effect of the anode of the polarizing current.

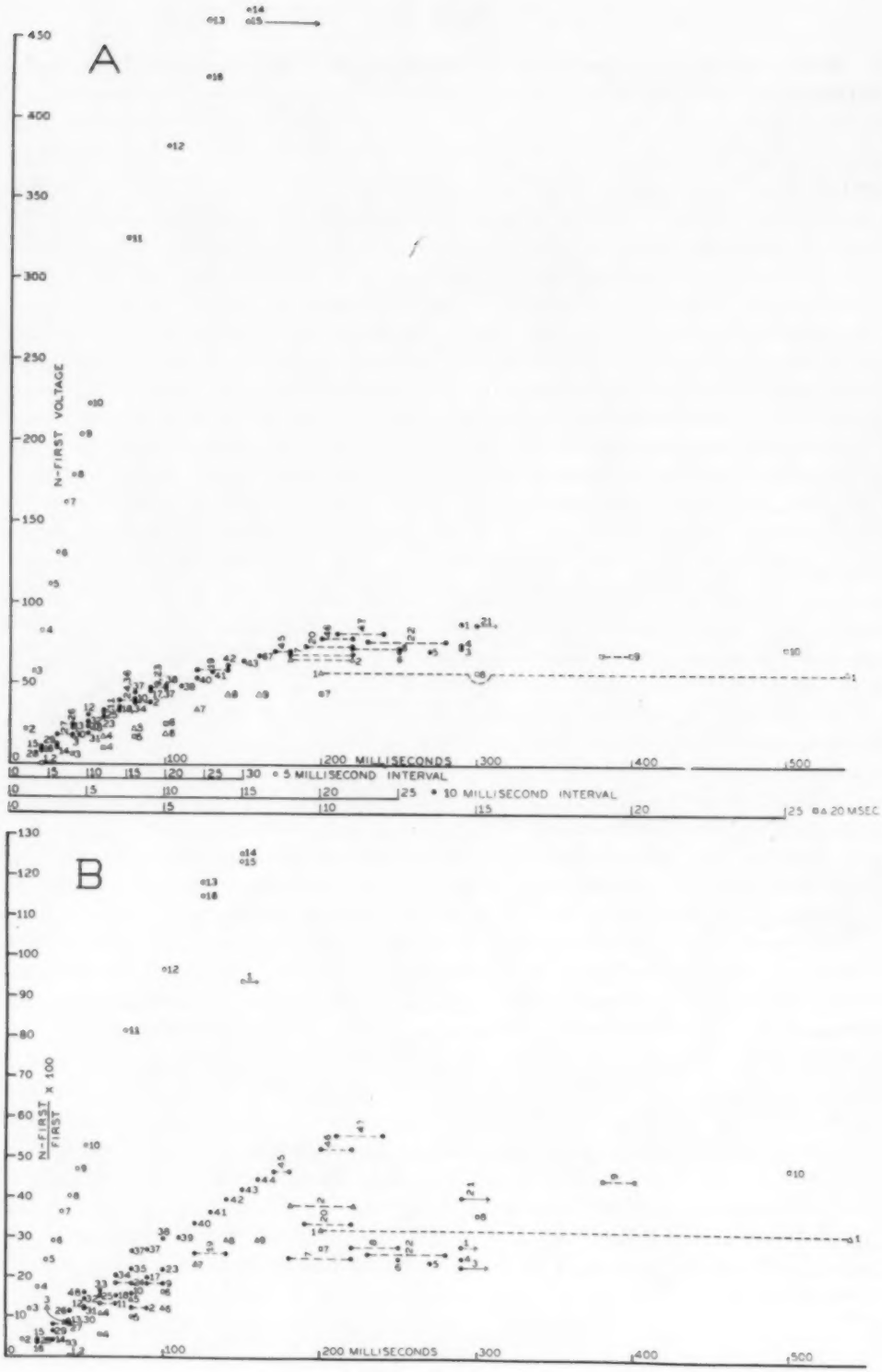

FIG. 5. (See next page for legend.)

We turn now to a consideration of those data. They are plotted in Fig. 5, in two ways, namely, in A, with

$$\text{Voltage to block } N \text{ spikes} - \text{voltage to block the first spike,}$$

and in B with

$$\frac{\text{Voltage to block } N \text{ spikes} - \text{Voltage to block the first spike}}{\text{Voltage to block the first spike}} \times 100$$

as ordinates, and with time as abscissae. Through the use of the second device it was hoped to achieve absolute results, but, in consonance with the foregoing considerations, it was found (as may be seen in Fig. 5, B) that determinations made late in a series are high, and that they are higher the larger the number of spikes blocked. In order to make this obvious in the graphs the individual determinations have been numbered in the order in which they were made. The first method mentioned above yields only relative results since with it the base line is constantly shifting, but they nevertheless are instructive. The curves show (1) that as many as 30 successive spikes can sum their effects across a block and (2) that the facilitation accomplished by the same number of blocked spikes at the rate of 200 per sec. may be six to eight times as great as that accomplished by spikes at rates of 50 and 100 per sec.

In order to get better information with regard to the effect of rate of stimulation on facilitation, experiments of a slightly different type were performed. Instead of making long series of determinations at each rate of stimulation, as was done above, the current strength was determined that was necessary to block a given, and the same, number of spikes at each of a few rates of stimulation, and the order of the determinations was staggered so as to make it possible to recognize any cumulative effect in time. In the case illustrated in Fig. 6, each tetanus consisted of but 15 spikes, and a

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FIG. 5. A. Graphs of the relation of the voltage needed to block N spikes minus the voltage needed to block the first spike (ordinates), to the number of spikes blocked. The tetanus consists of 40 spikes. Circles—5 msec. intervals between spikes; dots—10 msec. intervals; triangle and squares—20 msec. intervals. There was an interruption between the two sets of determinations at the 20 msec. intervals.

B is the same as A except that the ordinates are

$$\frac{\text{Voltage to block } N \text{ spikes} - \text{Voltage to block the first spike}}{\text{Voltage to block the first spike}} \times 100$$

In the case of the 10 msec. curve the voltage, through observation 27, was set arbitrarily and the number of blocked spikes determined; the spread of a reading between two spikes therefore is of no significance. Thereafter, and for all other curves, each reading is the threshold blocking voltage for the indicated number of spikes, and the width of the spread then is indicative of the diminishing facilitation per spike. Beyond about 25 spikes this spread is apt to extend out to the last, the 40th, spike, as indicated by the arrows. In many cases, however, no note was made of this spread.

current strength that blocked 10 to 11 of these was compared with the current strength that blocked 1 of them. The rates of stimulation used were 200, 167, 100 and 50 per sec., and the cycle period was 2.15 sec. The determinations at the different rates were made as expeditiously as possible. Otherwise the experimental procedure was as above.

During the course of the experiment the current strength that blocked one spike fell from an average of 621 in the first series of determinations (see the numbered points in the graph) to 286.5 in the 8th series. In Fig. 6 the results are plotted in the two ways mentioned above. When plotted by

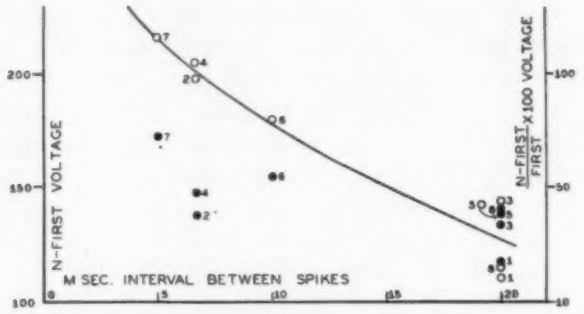

FIG. 6. Graph of the relation of the voltage needed to block N spikes minus the voltage needed to block one spike (circles and curve), and of

$$\frac{\text{Voltage to block } N \text{ spikes—Voltage to block the first spike}}{\text{Voltage to block the first spike}} \times 100$$

(dots), to the number of spikes impinging on the block per unit of time. The numbers indicate the succession of the determinations.

the N-First method the points fall nicely about a smooth curve with little if any evidence of an effect of the sequence of the determinations. It is seen that the facilitation effected by the 10 to 11 spikes at the rate of 200 per sec. is greater by about 71 per cent than that effected by the same number of spikes at the rate of 50 per sec. The shape of the curve is such as to indicate that facilitation would still be in evidence at very much slower rates than 50 per sec. and that it would increase rapidly at rates higher than 200. Qualitatively, facilitation by multiple blocked spikes is demonstrable with intervals of 100 msec.

The graph based on the per cent of the ratio, $\frac{N\text{-First}}{\text{First}}$, gives, again, very marked evidence of the disturbing effect of elapsed time, but when this is taken into account this method of plotting also shows that the facilitation is greater at higher than at lower rates of stimulation.

A fact of some interest in connection with these observations on the temporal summation by many successive spikes is that never are there any

interposed blocks in a tetanus, once facilitation has succeeded in overcoming the initial block. In view of the fact that the excitability of fibers is constantly fluctuating spontaneously through a range that usually amounts to about 5 per cent of the threshold, this unfailing response of the postfiber to the successive spikes, once it has begun to respond, signifies that with the first response something has transpired that immediately lowers the threshold of the postfiber by an amount that is greater than the spontaneous fluctuation in threshold. Undoubtedly what happens is that the successive spikes of the prefiber fall into the supernormal phases left in the postfiber by preceding responses.

Another factor which possibly assists in maintaining transmission, once the block has been overcome, is the background of a tetanus. Gasser's illustrations (1935) show that the negative after-potential in tetani comparable in rate and number of stimuli with those employed by us, may grow as the tetanus proceeds, so that both the peak potential and the potential of the background may rise, though the spike height remains constant. Though all spike potentials on this basis would be expected to send into the postfiber the same number of current lines, the growing negative after-potential, by continuously and increasingly polarizing the postfiber cathodally, would be expected to lower its threshold continuously, and so increase the effectiveness of the blocked spikes.

In the average experiment it is possible to adjust the blocking voltage so that a given number of spikes will be blocked regularly through a shorter or longer series of successive sweeps, as long as the number of spikes blocked is not in excess of about 10 to 15. Beyond that number the successive sweep pictures at any setting of the polarizing current exhibit varying numbers of blocked spikes, the variations being small at first but eventually very wide, so that a setting of the current that blocks, say, 20 spikes in one sweep, may block 40, or whatever the number available may be, in the next. These fluctuations are an expression of the spontaneous variation in the excitability of a fiber. As long as the summation increment per spike is in excess of this spontaneous fluctuation the successive pictures will be stable; and the instability will appear and increase as the successive summation increments fall to and below the range of the spontaneous fluctuations in excitability.

Difficilitation. When, with the rotor, a fiber is made to carry two relatively short bursts of spikes while it is being so polarized anodally at the lead that the spikes of the first burst are conducted through by facilitation, a spacing of the two bursts from each other can be found such that the second will require more spikes to overcome the block than the first (difficilitation), whereas a shorter spacing of the bursts can be found at which none of the spikes of the second burst will be blocked.

When, under conditions otherwise the same the first burst (through the hand-operated switch) is made a long one (2 or more sec.), a short intercalated period of no impulses (intervals of 0.5 to 1.0 sec. have been used) may be followed by block. If it is, recovery *ordinarily* will not occur as long

as the second tetanus is continued (the longest carefully checked period of second tetanization has been 43 sec.). But if this second tetanus is interrupted for a period of 6 or more sec. after it has been running for some sec. (5 or more), conduction through the block *usually* begins either at once with the resumption of tetanization, or after a relatively short period of facilitation. Apparently the second (but blocked) tetanus tends to maintain the difficilitation "indefinitely," whereas interrupting it temporarily permits of rapid recovery usually without the need of facilitation.

It may be inferred from the above summary that there must be many conditions affecting quantitatively the difficilitation obtained, such as the number of spikes needed for the facilitation of the first burst, the number of spikes constituting the first burst, the rate of stimulation, the intervals between the bursts, the changing effectiveness of the continuous polarization, fatigue, etc. The effects of these qualifying conditions have not been systematically investigated. Those conditions that can be controlled have been altered only in so far as has seemed to be necessary in the effort to determine which are fundamental to the development and continuance of difficilitation.

A description of the essential parts of an experiment in which both the rotor-operated and the hand-operated switches were used will serve to illustrate both the techniques employed and many of the characteristic reactions. There are many confirmatory observations, but none in which it has been possible to gather information from one and the same fiber under comparable conditions through the use of both the rotor- and the manually-operated switches, giving a reasonably wide range of stimulation and of rest periods. The stimuli were delivered at the rate of 74 per sec. With the rotor, the cycles recurred every 2 sec. The first burst (see Table 1) consisted of 23 or 24 spikes, and therefore lasted about 0.32 sec.; the second burst consisted of 15 spikes. At the outset the blocking potential was adjusted so that about two spikes were required for conduction in the first burst.

Table 1. Difficilitation by spikes. A second tetanus requires more spikes to overcome the the block than a first.

Record no.		1	2	3	4	5	6	7	8	9	11
No. of facilitating spikes in	1st tetanus	3	2	2	1–2	5	5–6	2–3	6–7	5	6–7
	2nd tetanus	7	10	9	10	10	9	9	10	10	10

By trial the two bursts were spaced by an interval that gave the maximum difficilitation obtainable under the circumstances; this interval was 0.52 sec. Narrowing the interval not only stopped difficilitation, it actually eliminated the need of facilitation in the second burst, the postfiber then responding to the first impulse of the second burst in the prefiber, but this limiting separation was not recorded. As may be seen in the table, the

number of spikes needed to establish conduction during the conditioning burst increased irregularly from about 2 to 6 or 7; for the testing burst it varied between 7 and 10. There was no obvious relation between the number of spikes blocked in the two bursts of a cycle, but with this separation the second burst always required more spikes to reestablish conduction than the first.

These particular conditions, therefore, yielded definite difficilitation. It can be shown, however, that the conditions here were far from the optimal for the development of the phenomenon. The important limiting circumstance was the duration of a cycle,—2.0 sec.; for at the optimal separation of 0.52 sec. between the first and the second bursts, the interval between the second and the first bursts was 0.6 sec. In other words, the latter interval was but little longer than the former, a state of affairs which must have resulted in making the difficilitatory effect of the second burst on the first almost as great as that of the first on the second. Moreover, this situation must have created a tendency toward the accumulation of difficilitation (subnormality), such as was noted in the first section of this paper. The more or less progressive increase in the number of the spikes needed for the facilitation of the first burst, mentioned above, probably was due likewise to this circumstance.

Then the hand-operated switches were employed. Here a "cycle" involved many sweep times, and it became necessary to develop a special technique in order to keep track of elapsed time and to observe transient phenomena. The spot occupied about 1.6 sec. in its transit across the face of the tube, and the returning intervals were about 0.4 sec. During each of these intervals a new frame of film was brought into position so that the whole of every sweep could be photographed. Though the pictures were thus taken discontinuously, the experiment continued without interruption. Each procedure was so timed that changes in imposed conditions occurred during a sweep, so that the immediate consequences could be observed.

The essential parts of one series of observations are reproduced in Fig. 7. The rate of stimulation and the amount of facilitation in the conditioning burst were about the same as in the first part of the experiment, the polarizing current being such that initially 7 spikes were required to overcome the block (sweep 1). This initial tetanus was continued without interruption for 6.3 sec. Then (sweep 4) stimulation was interrupted 0.68 sec. With the resumption of stimulation it is seen (sweep 4) that the impulses are blocked at the polarized locus: the change in the picture of a spike seen here is typical of block at the lead, in that the spike diminishes in height and becomes monophasic. This block persists through 5 sec. of stimulation. Stimulation then was stopped again (sweep 7) and was not resumed until 6 sec. had elapsed. It is seen (sweep 10) that with the resumption of stimulation the block has disappeared; not only this—conduction through the block now is accomplished without any facilitation. And though stimulation now was continued for 18 sec. there was no return of block. Since the polariza-

tion was maintained at a constant level throughout this experiment, this last step shows that the previous block could not have been due to increasing effectiveness of the anode polarization. It shows also that fatigue was not the determining factor in the maintenance of this block.

In the same experiment under similar conditions a tetanus lasting 8 sec. and a 0.72 sec. period of no stimulation were succeeded by "permanent" difficilitation also (it was followed for 11 sec.). Then an interpolated period of no stimulation lasting 14 sec. removed this block as above, and conduction continued thereafter until the experiment was discontinued, 16 sec. later.

Similar responses have been obtained in a number of preparations, but

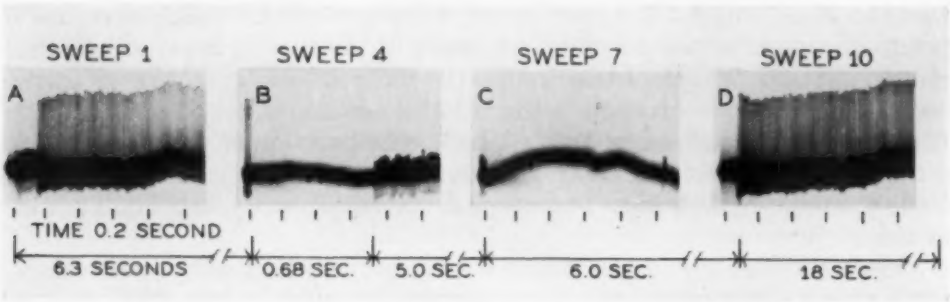

FIG. 7. Facilitation and difficilitation. Sweep 1 starts with the spike blocked at the lead. The 8th spike conducts through by facilitation; the spike not only becomes higher, but it becomes diphasic also. The positive, down, deflection during block is the shock artifact; at other times it is this plus the positive phase of the spike.

Sweep 4 begins with full spikes which have been continuing without interruption through sweeps 2 and 3 (not reproduced). During this sweep stimulation is interrupted for 0.68 sec. With its resumption the impulses are blocked.

Sweep 7, as it starts, shows this block still continuing. Then stimulation is stopped, and not begun again until—

Sweep 10. Here it is seen that with the resumption of stimulation the fiber conducts through again and without the facilitation needed at the start of sweep 1.

To gain space the sweep pictures have been cut on their left ends. The variations in spacing of the spikes are due to sweep irregularities and are without significance.

they cannot be demonstrated in all. Moreover, even in the case of the same preparation such results as are described above may be transient and inconstant. Extracts from the protocols of another experiment may be cited in order to illustrate an occasional variation from the rule.

In this case the switch was operated by hand. The rate of stimulation was 62.5 per sec. Only one fiber was responding. (i) Anode polarization was adjusted so that from 3 to 8 spikes were required for conduction. (ii) Without altering the polarization the preparation was allowed to rest for a time and then (iii) It was stimulated tetanically for a period of 8 sec. All impulses were conducted through. (iv) Then stimulation was stopped for 1 sec., and, (v) When stimulation was resumed all impulses were blocked. This period of stimulation, with continuous block, lasted 11 sec. (vi) Then stimulation

was stopped for 10 sec. (vii) On resuming stimulation block still was in evidence and persisted for 3 sec., when the impulses began to be conducted through.

It should be added that at another time in this experiment it had been possible repeatedly to demonstrate the usual result, namely, the immediate termination of "difficilitation" by a rest period. It may be worth mentioning also that in order to obtain facilitation and difficilitation in the present case it was necessary to add calcium to the Ringer's solution; this had not been necessary in the case of the first experiment cited above.

In these experiments conditions do not remain constant long enough to permit of the collection of satisfactory controls. This has made it impossible thus far to determine specific limits for the significant phases of the processes under investigation. Some of the extremes that have been observed have been given above, but it should be distinctly understood that they do not represent limits. An important qualifying factor must be the grade of the initial block and we have tried to hold this at the convenient level where 2 to 8 spikes were required for conduction. Under these circumstances we have seen "indefinite" difficilitation in response to a silence of 0.5 sec. following a tetanus of 2 sec., and in the same experiment no difficilitation following the same silent period after a tetanus lasting 1 sec.

Information regarding factors determining the duration of difficilitation is particularly incomplete. In the first place, we do not know how long difficilitation would have lasted (beyond 43 sec.) had the second tetanus been allowed to continue indefinitely. A 5 sec. interruption of tetanization of the prefiber usually has sufficed to allow impulses to pass when stimulation was resumed. But we have seen the difficilitation continue after a 24 sec. interruption of stimulation, and this in an experiment in which in several trials the fiber had conducted through immediately after very much shorter intercalated periods of rest.

Observations such as these should put us on our guard against a possible fallacy in the interpretation of the data. A period of no spikes may not curtail difficilitation. Instead, it is possible that a subnormal period following the first (the conditioning) burst has needed for its complete subsidence a period longer than the second tetanus, but shorter than the second tetanus plus the subsequent silent period. If the latter were the case the disappearance of the subnormal period could be disclosed only by supplying testing spikes during the second "silent" period. In other words, this question can be settled only by collecting a large number of comparative observations on the time required for the disappearance of the block initiated by momentary intermission of a tetanus under two conditions, namely: (i) when the second tetanus is continued indefinitely and (ii) when only occasional testing spikes are made to impinge on the blocked locus. Since we do not have that information all that can be said now is that in the present set of observations we have never seen a posttetanic block disappear while the spikes of a *second* tetanus were playing on it.

How may facilitation and difficilitation be accounted for? Facilitation undoubtedly is referable to an electrical effect exerted on the postfiber by the axon spike of the prefiber acting across the local discontinuity in the fiber. The known facts all support this view. Thus a subthreshold electrical shock immediately lowers the threshold, which then returns to normal through a period of over 50 msec. (Blair, 1938); and a series of subthreshold shocks as widely spaced as 20 msec. may sum their effects to cause fibers eventually to discharge (Gasser, 1938). Exactly the same effects with similar time relations are exerted on a postfiber by a blocked spike (Blair and Erlanger, 1939), and, as described in the present paper, by a series of blocked spikes.

Difficilitation (or at least the first of its phases, assuming that there are two) finds a simple explanation in the subnormality of the postfiber into which the latter passes subsequent to the termination of a conditioning tetanus; the block that has been overcome by facilitation is easily reestablished, and is reestablished by failure of the spike of the prefiber, acting electrically, to attain the threshold of the subnormal postfiber.

The question now arises, is there a second phase to difficilitation which accounts for the apparent fact (discussed above) that once difficilitation has been induced the postfiber will not ordinarily carry impulses during the continuance of the tetanus in the prefiber? To what might such a protraction be due? Subnormality of the height of the spikes in the prefiber can be eliminated, since the height of the blocked spikes of the second tetanus is the same, as nearly as it can be measured, as that of the spikes blocked by anode polarization at the start of the conditioning tetanus before conduction through the block has been established by facilitation.

Is it, then, referable to some depressing influence exerted by the tetanized prefiber on the postfiber? Two possibilities suggest themselves in this connection. (i) The prefiber not only supplies spikes, but these spikes in addition ride on the background of the negative after-potential. The negativity of the after-potential, like that of the spike, must lower the threshold of the postfiber through electrical action. If, therefore, the background of a second tetanus following a first after a few seconds were lower than that of the first it is quite conceivable that this might suffice to maintain a block which otherwise would have disappeared. However, facilitation, as has been seen, can lower thresholds quite materially, and it seems rather unlikely that any deficit there might be in the negative after-potential background of such a second tetanus would be sufficient to overcome the facilitating effect of the spikes. It does not, however, seem profitable to pursue this idea further, since data on the background potential of a tetanus initiated during the positive after-potential following a previous tetanus seem to be entirely lacking.

(ii) The other possibility that occurs to us is that repeated subthreshold spikes (and electrical stimuli) may maintain continuously the elevated threshold that obtains in the postfiber during the subnormal phase of its excitability cycle. There is available no specific information bearing on

this suggestion, either, and it may, therefore, be somewhat gratuitous to say that such a depressing action would constitute inhibition, and would put inhibition on an electrical basis.

There is to be considered also the possibility that rest hastens recovery from difficilitation by permitting the prefiber to deliver impulses which are stronger than those developed during a continued tetanus. This thought is suggested by the fact that the initial spike of the third tetanus in sweep 10 of Fig. 7 is higher than the first full spikes of sweep 1 (though the height of the spikes of sweep 10 quickly decrement before starting a treppe). But the prefiber contributes relatively little to the recorded height of a spike that is conducted through, so that the increase seen here while the spike is blocked, must be a contribution of the postfiber, primarily. If, however, the first spike of the prefiber is increased to the same extent as is the spike of the postfiber it still might be possible to refer the recovery from prolonged difficilitation that occurs after a period of no stimulation to that rather than to anything that is transpiring in the postfiber.

Extinction. Dusser de Barenne and McCulloch recently (1935 and 1939) have described the phenomenon of "extinction" which they define as (p. 320) "a diminution or absence of response on repetition of stimulation of a 'motor' focus within an interval longer than that required for facilitation." These authors believe that extinction is not due "merely to the passage of a stimulating current" since it does not occur unless the electrical stimulation elicits a neural response. Extinction then is a process that takes place at a synapse and has the same electrical basis as the "difficilitation"* we have demonstrated at a discontinuity in a nerve fiber. It is of interest to add that extinction is associated with local electropcsitivity.

Recruitment and disbandment. That the blocked spikes act *electrically* to produce facilitation and to influence difficilitation is indicated by experiments we have made on the responses of fibers to direct electrical stimulation. Here the stimuli are shocks and the "discontinuity" consists of the junction of the electrical circuit with the nerve fiber, whereas in the former case the stimuli are spikes acting across a discontinuity in the fiber. Comparative observations have been made only with the rotor-operated keys. Pictures obtained by the two methods, showing recruitment (or facilitation) and "disbandment" (or difficilitation), are identical in every respect save one: when the relevant events transpire at the stimulating electrodes no part of the spike is visible during the periods when the shocks are below the threshold, only the shock escapes appearing in the records, whereas when there are impulses which are blocked at the lead, the spike potential is recorded, but in reduced amplitude, as well as the shock escape.

* We prefer the term "difficilitation" to "extinction." For though facilitation and extinction (difficilitation) are not, as these authors state, antagonistic phenomena (since they are successive), they are so as regards the effects they produce. Thus a block in a fiber that has been overcome by facilitation is reestablished by difficilitation. And in the case of the central nervous system the one process increases action, the other decreases it.

Though the results obtained in the present experiments might have been anticipated on the basis of what is known regarding the excitability cycle, they do throw light on some questions of interest. One set of observations, therefore, will be described and illustrated (see Fig. 8 and Table 2). The polarizing current here is dispensed with. The preparation contained three fibers that conducted to the lead. The spike of fiber A was high and recorded

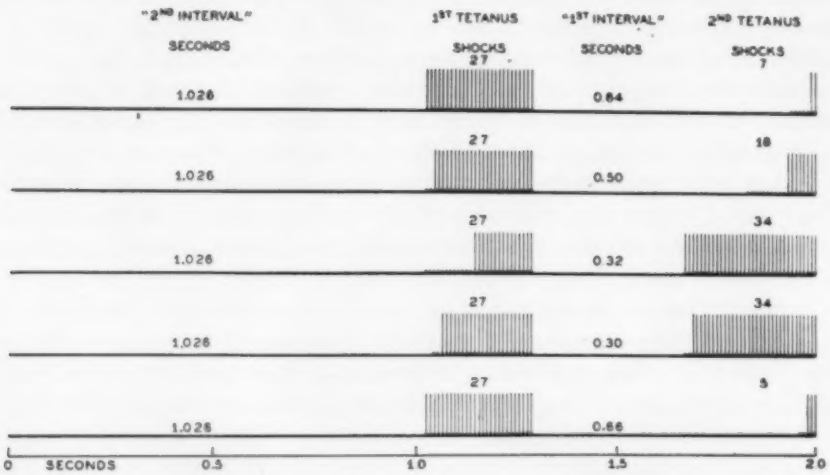

FIG. 8. Diagram showing recruitment (facilitation) and "disbandment" (difficilitation) in fiber A (table 2), effected through direct electrical stimulation. Each horizontal line is a conventionalized, but accurate reproduction of a cycle. For the sake of clearness the second interval between tetani is placed ahead of the "first" tetanus. The rate of stimulation is 80 shocks per second. Each shock is indicated by a dot; those surmounted by lines reached the threshold of the fiber.

monophasically, that of B diphasically, while fiber C responded somewhat irregularly with a low monophasic spike. C was difficult to recognize in certain situations; consequently its behavior will not be considered. It may be added, though, that when it responded it was always by facilitation, never with difficilitation. The rotor-operated switches were employed to deliver two tetanic bursts of shocks at the rate of 80 per sec. The cycle occupied 2.15 sec. The first burst consisted of 27 shocks; the number in the second varied as the interval between the first and second bursts changed, so that the intervals between the second and the first bursts in the successive cycles remained essentially the same throughout (1.026 ± 0.04 sec.). The shock employed at the start was just about threshold for fiber A so that in the first burst of a cycle A usually responded to the first shock.

The diagram (Fig. 8) shows clearly that in the case of fiber A difficilitation (negative recruitment or "disbandment") is greatest when the interval between the first and the second bursts is 0.5 sec., and is nearly or quite absent both at narrower (0.3 sec.) and at wider (0.66) intervals. In Table 2 it may be seen that fiber B behaves similarly, though not so obviously. The

resting threshold of B was higher than that of A, as is indicated by the larger number of shocks needed to reach the threshold during the first burst. Indeed, in most of the trials so many were needed that the number of effective shocks in the testing burst was fewer than the total in the conditioning burst, so that difficilitation, if present, had no opportunity to

Table 2. Recruitment (facilitation) and "disbandment" (difficilitation) by electrical stimulation in two fibers, A and B.

Record No.	Time bet. 1st & 2nd Tetani	Time bet. 2nd & 1st Tetani	Shocks in 1st Tetanus	Shocks in 2nd Tetanus	Facilitating Shocks in 1st and 2nd Tetani			
					Fiber A		Fiber B	
					1st	2nd	1st	2nd
	sec.	*sec.*						
1	0.64	1.073	27	7	0	1	13	7+
2					0	7+	14	7+
3					0	4	14	7+
4					0	3	9	7+
5					0	7+	14	7+
6					0	7+	14	7+
7	0.5	0.983	27	18	0	9	23	2
8					1–2	11?	27+	11
9					1	9	11	13
10					0	12	14	14
11	0.32	1.060	27	34	14	0?	25	0
12					13	0	27+	34+
13					13	0	27+	25
14					16	0	23	0
15	0.3		27	34	1–2	0	27+	25
16					1–2	1–3?	17	0
17					1–2	0	27+	25
18					1–2	0?	13	0
19	0.66	0.989	27	5	0	2	4	5+
21					0	0	10	5+
22					0	2	3–4	5+
23					0	0	6	5+
24					0	3	13	5+
25					0	0	9	5+
26					0	1	13	5+
28					0	0	10	5+

"Disbandment" is indicated where the second tetanus requires more shocks for effective stimulation than the first. A plus sign signifies that the total number of shocks available did not suffice to reach threshold. When, in such instances, the number of shocks in the second tetanus is smaller than the number in the first it is not possible to know whether difficilitation would have obtained. The decrease in the number of shocks needed for recruitment in observations 15 to 18, as compared with observations 11 to 14 (first tetanus of fiber A), was determined by a slight increase in shock strength; it was made in order to reduce the increased number of shocks required for facilitation, an increase due probably to enhancement of subnormality by the increase in the number of spikes in the second tetanus.

exhibit itself. The few instances where the number does suffice for stimulation, indicate that the maximum of difficilitation occurs at about the same interval between bursts, namely, 0.5 to 0.66 sec., as in the case of fiber A.*

It is obvious then, that both subthreshold shocks and axon spikes that become effective through facilitation during a first tetanus act alike in respect to facilitation and to difficilitation. Now in the case of direct electrical

* This description omits consideration of certain unessential, but interesting features.

stimulation a background potential in a prefiber (here represented by the coil circuit) does not obtain. It follows that where impulses are impinging on an anode block, a reduced background potential in the tetanized prefiber is not an essential condition for the development of difficilitation. And it may be concluded that difficilitation, in its initial stages at least, is determined only by subnormality of the postfiber.

SUMMARY

At a discontinuity (block) in a nerve fiber created by anode polarization, a discontinuity that can be graded by varying the strength of the polarizing current, it is possible to demonstrate and to gauge the facilitation effected by blocked action potentials and to demonstrate a phenomenon, designated difficilitation, which probably is identical with "extinction."

The facilitating action of spikes at such an artificial synapse increases with their number and with their frequency. The facilitation per impulse declines slowly with the number, but is demonstrable through at least 20 impulses. The facilitating action has not attained its maximum at impulse rates as high as 200 per sec., nor its minimum at rates of 10 per sec.

Once, in a tetanus, a spike succeeds in passing a block, all of the succeeding spikes of that burst also will pass, notwithstanding the spontaneous variations in the excitability of a fiber. This effect is attributed to the supernormality that follows immediately the response of the postfiber.

Difficilitation is demonstrable, when conduction has been established by facilitation, by interrupting this conditioning tetanus momentarily, the optimum period of interruption (under a specific set of conditions) being in the vicinity of 0.5–0.6 sec., when, upon resumption of the tetanus, it may happen that spikes will no longer pass from the prefiber to the postfiber (i.e., across the local discontinuity) as long as the tetanus continues. (Observations on this interruption of conduction have not been continued longer than 43 sec.) But interrupting the second tetanus for a period of 6 sec. seems to permit the block to disappear.

Difficilitation, at least in its initial stages, is regarded as a manifestation of the subnormal phase of the excitability cycle in the postfiber a cycle that is started by the momentary interruption of tetanic stimulation; the spikes of the prefiber, with the resumption of tetanic stimulation, then no longer reach the threshold of the postfiber.

Exactly the same phenomena of facilitation (recruitment) and of difficilitation (negative recruitment or "disbandment") are demonstrable at the site of stimulation of a fiber with induction shocks, and it is concluded that both facilitation and difficilitation result from the spike's action as an electrical stimulus to the postfiber. This holds not only with regard to the artificial synapse in the nerve fiber but, by inference, with regard to the actual synapse, as well.

The protraction of difficilitation which *seems* to be determined by con-

tinued tetanic stimulation of the prefiber is discussed, but no conclusion is reached regarding processes that might be determining it.*

* Since this paper was submitted for publication there has appeared a paper by Lorente de Nó (*J. Neurophysiol.*, 1939, *2:* 402–463) dealing with some of the questions we have had to consider, such, for example, as the extension of after-potentials beyond blocks. Unfortunately it will be impossible now to take further cognizance of Lorente's paper.

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A HUMAN CORTICAL AREA PRODUCING REPETITIVE PHENOMENA WHEN STIMULATED*

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DURING the electrical exploration of a human cortex, an area was found which, when stimulated, resulted in perseveration of speech. The nearest approach to this in the literature appears to be an experience of Penfield's, in which a patient who was counting "seemed to continue the eleven sound" at the moment of stimulation. The stimulated point in Penfield's case was in the motor area, on the lateral side of the left hemisphere, near Broca's area,—a long distance from the zone which is the subject of this report (1, p. 426).

The patient, referred by Dr. Henry Hart, was a 32 year old, right handed, white American woman, who had had grand and petit mal since the age of 17. It was decided to explore her cortex electrically according to the technique of Penfield (1), in the hope of discovering a trigger area which might be removed. The operation was performed on March 15, 1939, under novocaine anesthesia, by Dr. Clement Masson. The exploration was made on the left side. The scalp was unusually poor in vascularity. A left fronto-parietal flap was turned. The edges of the bone were found to be between 2 and 3 cm. in thickness. The bone was less vascular than usual. The subdural space contained a rather excessive amount of fluid. The cortex appeared more vascular anterior to the precentral gyrus than posterior to it. The Rolandic vein was much enlarged. In the precentral sulcus lay another equally large vein. These veins converged and entered the longitudinal sinus at adjacent points. The anterior vein was ligated near the sinus and also at the lower edge of the bone flap,—about over the middle frontal convolution.

Stimuli were delivered through a two-point electrode, from a thyratron stimulator (controlled by Dr. Robert Laidlaw) operating at 50 cycles per second and 50–100 volts. Three to four milliamperes were put out, but, because of a partial short circuit in the electrode, the exact amount delivered to the patient cannot be stated.

Areas 1, 2, 3, 4, 5 and 6 were stimulated quite extensively on the lateral, and 4 and 6 on the mesial surface. Sensory and motor points were mapped out, but no trigger zone was found. The brain was very gently retracted laterally, so that the electrode points could be placed upon its mesial surface. Additional sensory and motor points were there determined. The area which is the subject of this report, and which will be alluded to as area X, lay on the mesial surface of the left hemisphere, low down in area 6, probably just above its junction with the posterior tip of area 32 (Fig. 1). The zone was a little less than 1 cm. in diameter. It was discovered accidentally, during the routine exploration. The patient suddenly uttered syllables resembling, "err, err, err," in what seemed a stereotyped manner. The area stimulated at that moment was noted.

The patient thereupon obeyed the examiner's request to say the alphabet. As the recital proceeded area X was repeatedly stimulated for periods of several seconds. Each time this was done, the letter being uttered at the moment of application of the stimulus was repeated. The repetition continued throughout the period of stimulation, ceasing instantly

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upon termination of the stimulus, when the ordinary saying of the alphabet was immediately resumed. The repeated letters were slightly distorted, and their rate of production was perhaps slightly slower than the rate at which the patient spoke the rest of the alphabet. The phenomenon is exemplified in the following quotation from the patient. The italics represent the application of the stimulus. "A B C D E F G *H H H H H H* I J K L M *N N N N N N N* O P Q *R R R R R* S T U V W X Y Z." The performance could be repeated at will, and was carried out eight or ten times.

The patient, on questioning, said that she was fully aware of what was occurring, but was unable to check herself. No feeling of discomfort or other special sensation was experienced. The patient's condition was excellent throughout. Because of the rather excessive amount of electrical stimulation which had been given, it was considered best to ter-

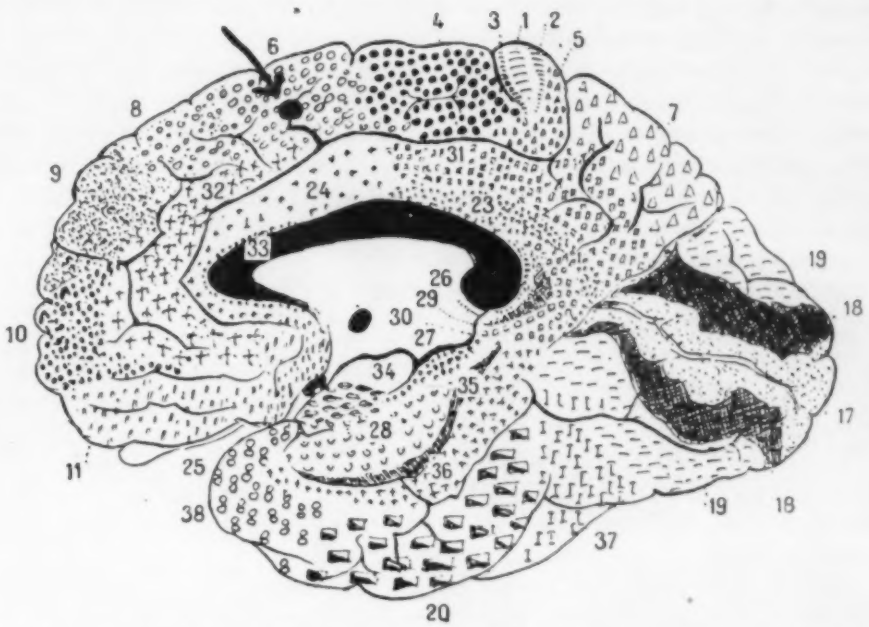

FIG. 1. The approximate position of area X is indicated by the black disc (arrow).

minate the procedure without undertaking the numerous additional tests which might have been made.

After cauterization, area X was excised to a depth of about 0.2 cm., the entire specimen measuring about 1 cm. in diameter. After the excision, stimulation of the exposed white matter, and of the cortical edges, failed to elicit the phenomenon. The specimen was fixed in formalin. Sections stained with hematoxylin and eosin and examined by Dr. Abner Wolf showed no changes which could not be explained by the surgical procedures.

Although the observation has, thus far, been made in only one case, it is none the less real. A point which must not be lost sight of is that the brain was not strictly normal. Not only was there a convulsive state, but also the bone of the vault was extremely thick, and there were two veins, one or both of which were abnormal. In addition, one of these veins had been ligated prior to the stimulation. The ligation, as such, produced no noticeable symptoms, at least nothing immediate.

These considerations bring up the question of whether such an area as X can act upon normal brain tissue, whether an abnormality must be present in a zone for X to influence it in this way, or whether X itself must be abnormal for the effect to occur. Such questions as these may find answers in further study.

Discussion

No known part of the speech zone lies near area X. The nearest cortical part, Broca's area, is 8.5 cm. away, as measured directly through the substance of a slightly atrophied brain fixed in formalin. Therefore, apparently normally acting cells of the brain were influenced, and caused to act abnormally, by stimulation of other cells a considerable distance away. The particular form of induced abnormal activity was one in which certain cells were thrown into function again and again. It was as though the nerve impulse were imprisoned in a given cell group, able to activate that group only, and unable to pass to another group. The situation recalls the "closed circuit" theory, propounded by Kubie (2) and others (3, 4, 5, p. 152) and elaborated by Lorente de Nó. (7), and can be analyzed in terms of circuit reactivation.

Summary

During the electrical exploration of a human cortex, an area was found which when stimulated, produced perseveration of speech. The area (area X) lay on the mesial side of the left hemisphere, in area 6, probably just above the junction of that area with the posterior part of area 32.

The patient, under local anesthesia, said the alphabet. At each application of the stimulus, and throughout the period of stimulation, the letter the patient was saying was repeated over and over again. The perseveration ceased instantly when the stimulus was stopped.

Area X is far from any known part of the speech zone. It influenced the function of distant neurons, and in such a way that these neurons were thrown into action again and again, as though the impulse were imprisoned in a given cell group, able to activate that group only, but unable to pass to another.

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EFFECTS OF ESERINE, ACETYLCHOLINE AND ATROPINE ON THE ELECTROCORTICOGRAM

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IN A RECENT PAPER (Miller, 1937) it was shown that eserine in 1 per cent solution exerts a local excitatory effect on the cerebral motor cortex of the cat: the manifestations consist of tremors and rigidity in the limb controlled by the cortical area, to which the eserine is applied. It appeared to be of interest to determine the possible effects on the electrocorticogram (Dusser de Barenne, McCulloch and Nims, 1937; Dusser de Barenne and McCulloch, 1938) of the application of this drug: on trial it was found that eserine alters the potentials profoundly. In a logical extension of these experiments it was ascertained that acetylcholine (ACh) applied in low concentrations to the cortex, previously eserinized, evokes extraordinarily large, rapid spikes.

Sjöstrand (1937) had shown that the application of ACh to the cortex, following strychnine and eserine, evokes fast regular waves. Bonnet and Bremer (1937a) observed that minute intra-arterial doses of ACh augment the after-discharges of spinal reflexes in the frog; larger doses are merely depressant. Bonnet and Bremer (1937b) and Bremer (1938) also studied the changes in the brain potentials of the rabbit induced by the injection of ACh into the carotid artery: minute doses increase the amplitude and frequency of the waves and also cause general excitation of the animal; larger doses depress or abolish the waves.

Our own researches, pursued independently, differ materially from those of others: thus the effects of eserine and ACh on the potentials were studied individually and without strychnine; further, the local effect of ACh was tested on the cortex, previously eserinized. A short, preliminary report of our work was given before the American Physiological Society in March, 1938 (Miller, Stavraky and Woonton, 1938).

METHODS

Our observations were made on 18 rabbits and 12 cats. Anaesthesia was secured with dial, 0.5 cc. per kg.; the total amount was injected intraperitoneally or half intraperitoneally and half intramuscularly (Dusser de Barenne and McCulloch, 1937). Recording was by the bipolar method with one electrode on the frontal, the other on the occipital region of the cerebral cortex; a pair of electrodes was often applied to the opposite cortex for simultaneous recording. Electrodes were of the Ag, AgCl, camel hair brush or absorbent cotton types. Each pair of electrodes was connected with a 4-stage vacuum tube amplifier, operating a cathode ray oscillograph (Radio Corporation of America, Type No. 907). Controls from the brain of the dead animal at the conclusion of each experiment showed that the systems were free from artifacts.

The drug solutions were sometimes applied to the cortex in small squares of "spot test" paper; each square was 4 mm. on the side. At other times application was made by dabbing or painting with a fine camel hair brush. The following drugs were used: eserine sulphate (Burroughs Wellcome & Co.); acetylcholine bromide (Eastman Kodak Co.);

atropine sulphate (Merck); pilocarpine hydrochloride (Merck); the drugs were dissolved in Ringer-Locke's solution, containing 0.02 per cent $NaHCO_3$.

Determinations of the pH of solutions. Determinations of the pH of the Ringer-Locke solution and of the drug solutions were made with a Beckman pH meter (glass electrode). The pH values are as follows:—

Ringer-Locke	7.3
1 per cent eserine in Ringer-Locke	6.6
1 per cent ACh in Ringer-Locke	7.3

The close similarity of the pH of 1 per cent ACh in Ringer-Locke's solution to that of Ringer-Locke's solution itself may be explained by the buffer action of the latter solution on the slightly ionized HBr of the acetylcholine bromide. The Ringer-Locke's solution was brought with 0.1 *N* HCl to 6.6, the pH of 1 per cent eserine, and was used as a control for eserine.

Controls with saline. Any possible electrical effects through conductivity changes between the electrodes were controlled by preliminary irrigation with saline and by the application of a paper square soaked in saline. These procedures yielded none of the effects observed by the drug applications.

Results

For purposes of analysis and description of the effects of the drugs on the electrocorticogram we have defined the three following classes of waves, setting in each class arbitrary limits on period: (i) *Slow waves;* period 0.1–0.75 sec. (s, Fig. 1A). (ii) *Fast waves;* period 0.025–0.09 sec. (f, Fig. 1A).

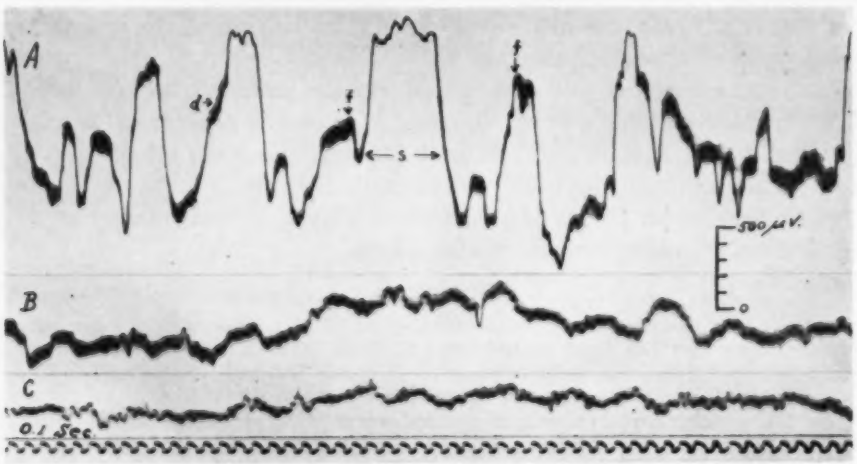

Fig. 1. Effects of eserine on electrocorticogram. Rabbit. Dial. Electrodes 10 mm. apart, one anterior, other posterior on cerebral cortex.

A. Before eserine; s, slow wave; f, fast wave; d, dot wave.

B. 1 min. after application with small brush of 1 per cent eserine to cortex between electrodes. Reduction in amplitude of slow waves.

C. 4 min. after 1 per cent eserine. Progress of eserine effect.

(iii) *Dot waves;* slight discontinuities in sweep of fluorescent spot; period 0.01–0.02 sec. (d, Fig. 1A).

Effects of eserine. The application of 1 per cent eserine to the cortex causes, within 1–2 min., a progressive reduction in amplitude of the slow waves and of the large fast waves; at the same time the small fast and dot waves become more apparent, possibly because of the reduced amplitude of the slow waves (Fig. 1 and 2). The above effects continue for approximately 30 min. after application of eserine. Accompanying the above electrical changes it is usually possible to observe motor phenomena, indicating cortical stimulation: these include muscular tremors and twitchings; they are more marked from eserine on the motor cortex of the cat, when the opposite fore- and hindleg are rigidly flexed and exhibit tremors (cf. Miller, 1937).

Control observations on the possible influence of pH differences were made by applying, to the cortex of the rabbit and cat, Ringer-Locke of the same pH as 1 per cent eserine, namely 6.6; this was found not to yield the characteristic effects of 1 per cent eserine, there being no detectable change in the potentials. Dusser de Barenne, McCulloch and Nims (1937) have shown that lowering the pH of the cortex itself reduces the electrical activity. The absence of change in potentials from reduced pH in our experiments may be attributed to the circumstance that the solutions were applied to the cortex in minimal quantities; these would mix with the larger volume of the cortical fluid, which would afford considerable buffering. Thus, in our experiments, it appears unlikely that the pH of the cortex itself would be changed. Hence the effects of eserine application may be regarded as due to specific drug action and not to lowered pH.

Effects of ACh on the non-eserinized cortex. As contrasted with the powerful effects of ACh on the eserinized cortex to be described presently those on the non-eserinized cortex are slight. In a few experiments, in which the cortex of the rabbit had been exposed under 1–2 per cent procaine (Merck), 0.2–1 per cent ACh applied locally reduced slightly the amplitude of the slow waves. A reduction in amplitude of the slow waves was also yielded by the application of $1:10^5$ ACh to the motor cortex of the cat under dial. These effects thus resemble those of eserine, although they are much less pronounced.

Effects of ACh on eserinized cortex. The consequences of the application of ACh to the eserinized cortex are similar in the rabbit and cat. The designation of the areas of the rabbit's cortex in the legend of Fig. 2 are according to Rose (1931). Eserine in 1 per cent solution is applied to the cortex and the effects above described are induced (Fig. 2B; 3B). While these responses are continuing a square of 1 per cent ACh is applied to the cortex between the electrodes: within 30 sec.–2 min. large, rapid, rhythmical waves appear (Fig. 2, C; 3, C). Each wave is a complex consisting of two diphasic spikes with smaller components superimposed; the spikes themselves we designate the Es-ACh spikes (Sp.). In Fig. 2 there are 10 complex waves/sec.; the average amplitude of the spikes above and below the isoelectric

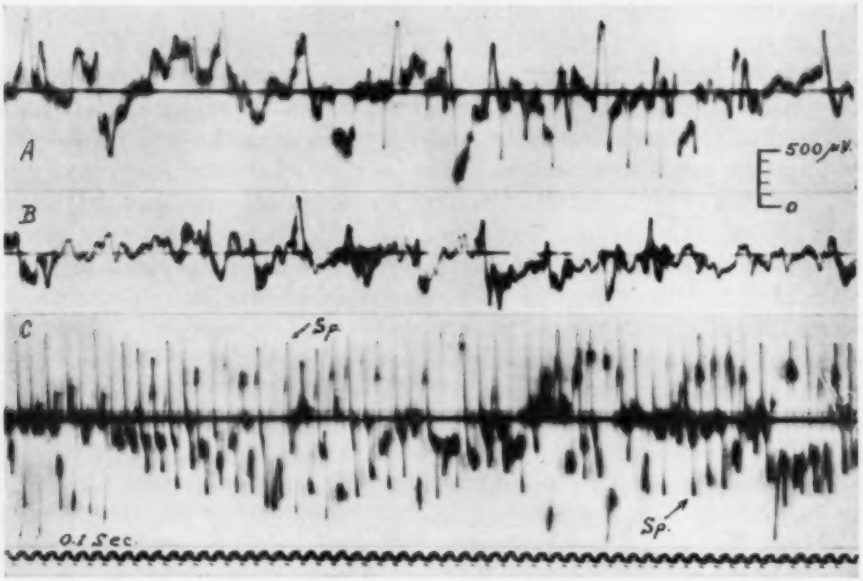

FIG. 2. Effects of eserine and ACh on electrocorticogram. Rabbit. Dial. Electrodes 17 mm. apart; anterior electrode on *regio praecentralis granularis* (Rose), posterior electrode on *area striata* (Rose).

A. Before drugs.

B. 3 min. after application of square of 1 per cent eserine midway between electrodes and painting cortex with small brush of 1 per cent eserine. Reduction in amplitude of slow waves and of large fast waves.

C. 1 min. after application of square of 1 per cent ACh midway between electrodes. Sp., Es-ACh spikes. Vibrissae movements occur. Spikes began 30 sec. after applying ACh.

line in Fig. 2 is 650 μV. In Fig. 3 there are 8 complex waves/sec.; in this case the average amplitude of the spikes above the isoelectric line is 500 μV., while the average amplitude of those below the same line is 250 μV. The spikes resemble in appearance the strychnine-spikes described by Dusser de Barenne and McCulloch (1936).

In another experiment a square of 0.2 per cent ACh was applied midway between the electrodes to the eserinized cortex of a rabbit under dial; in 30 sec. periodic bursts of Es-ACh spikes developed. The first square of 0.2 per cent ACh was then replaced by a second of 0.2 per cent ACh, whereupon the spikes at once appeared continuously and also motor effects, consisting in vibrissae movements.

A matter of importance is the proof that in order to evoke the Es-ACh spikes it is essential that the application of eserine *precede* that of ACh; the reverse order fails to evoke the spikes. Thus, for their production, ACh must act on the eserinized cortex. Control records from the opposite cortex indicate that the effects of both eserine and ACh are due to local action on the cortex. Indicative of cortical stimulation, motor effects, more intense than those from eserine alone, often accompany the Es-ACh spikes: they are

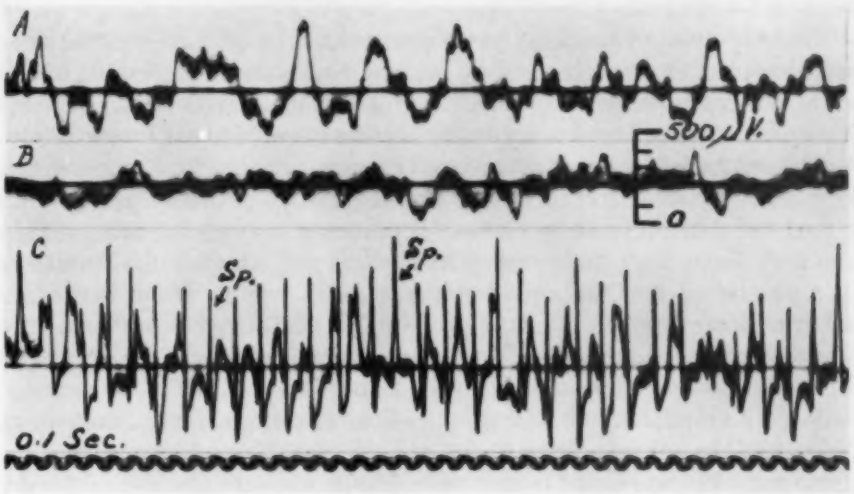

FIG. 3. Effects of eserine and ACh on electrocorticogram. Cat. Dial. Electrodes 22 mm. apart; anterior electrode on anterior sigmoid gyrus, posterior on suprasylvian gyrus.

A. Before drugs.

B. 4 min. after square of 1 per cent eserine and painting cortex with 1 per cent eserine. Eserine effect.

C. 5 min. after square of 1 per cent ACh on posterior sigmoid gyrus. Sp., Es-ACh spikes.

more evident in the rabbit, in which they consist of vibrissae movements, tremors and mastication; the latter was observed in the rabbit under procaine during the incidence of the Es-ACh spikes; it was due to stimulation of the cortical area of mastication (Ferrier, 1886).

Prevention of Es-ACh spikes by atropine. The influence of atropine was examined in the rabbit by the intravenous injection of 4 mg. (in a rabbit of 3400 g.) and the local application to the cortex of a 0.2 per cent solution of this drug. In this state of complete atropinization the subsequent applications of 1 per cent eserine and 1 per cent ACh fail to evoke the Es-ACh spikes.

Pilocarpine. It was decided to test the effect of another parasympathomimetic drug, namely pilocarpine. The application of 1 per cent pilocarpine to the cerebral cortex of the rabbit does not yield any appreciable changes in the electrocorticogram. Also the subsequent application of 1 per cent ACh fails to evoke waves like the Es-ACh spikes. Thus, pilocarpine is not a sensitizer for ACh as is eserine.

DISCUSSION

When 1 per cent eserine is applied to the cortex it diffuses in small amounts into the cell layers; there, according to evidence presented in an earlier paper (Miller, 1937), it facilitates transmission at cortical synapses, revealing its action by characteristic muscular responses; this facilitation

appears to be of the nature of stimulation of the synaptic junctions. Since muscular responses of the kind mentioned accompany the eserine electrical effects, these latter may themselves be regarded as manifestations of stimulation of cortical synapses by eserine. The synaptic stimulation by eserine may be due to direct action by the drug; however, it will be recalled that ACh evokes, from the (non-eserinized) cortex, effects like those of eserine, namely a slight reduction in amplitude of the slow waves. Hence, we may infer that ACh stimulates synapses; also that the synaptic stimulation by eserine may depend on its known property of inhibiting cholinesterase, with resulting lessened destruction of natural ACh, which would serve as the actual stimulating agent.

We may now consider the electrical effects of the application to the cortex of 1 per cent eserine, assuming it to be an excitant of synapses. The reduction in amplitude of the slow and of the large fast waves may be attributed to the asynchronous firing of large numbers of neurones and this, in turn, may be ascribed to the stimulation by eserine of multitudes of synapses, to widely differing degrees. These differences in synaptic stimulation will depend on the concentration gradient of eserine as it diffuses below the cortical surface; on variations among synapses in susceptibility to the drug; and on numerical differences in synapses in different cortical layers (Lorente de Nó, 1938). In consequence of the above factors asynchronous firing of the synaptically controlled neurones ensues: this is observed as reduction in amplitude of the waves. Conditions are somewhat analogous to those in the optic ganglion of *Dytiscus*, in which faint light abolishes the large waves of the dark rhythm (Adrian, 1937).

ACh when applied to the eserinized cortex, evokes both the Es-ACh spike potentials, as well as the pronounced motor effects described above; both responses may thus be regarded as evidences of cortical stimulation. They illustrate the close interaction generally recognized as existing between eserine and ACh. Reasons have already been given for believing that ACh alone stimulates synapses; thus we may infer that ACh stimulates more intensely synapses previously eserinized; this stimulation being powerful will tend to be of equal intensity at large numbers of synapses and, in consequence, there will result synchronous activity of multitudes of neurones, with the electrical accompaniment of the Es-ACh spikes.

With bipolar recording the spikes above the isoelectric line indicate synchronization of neurones under one electrode, the spikes below the same line synchronization under the other electrode; thus the subelectrode synchronizations are largely out of phase with each other. In Fig. 2 the approximate equality of the spikes above and below the isoelectric line is dependent on the paper square of ACh being placed midway between the electrodes. On the other hand, the greater amplitude of the spikes above the isoelectric line in Fig. 3 is the consequence of the proximity of the ACh square to the anterior electrode.

In the process of neuronal synchronization through synaptic stimula-

tion by eserine and ACh the cells with short axons may be conceived as playing an important rôle for several reasons: each of these cells controls a large number of pyramids and is itself the site of termination of many synapses; further, these cells exist in every cortical layer (Lorente de Nó, 1933; 1938).

That preliminary atropinization prevents the development of the Es-ACh spikes may be interpreted as an instance of the known property of atropine of precluding the effector response by ACh; we would mention also that certain observations, which we have made, indicate as well the possibility of a direct antagonism between eserine and atropine. In general our results with atropine afford substantiation for our views that ACh stimulates eserinized synapses. The highly specific nature of the actions of eserine and ACh is emphasized further by the failure of pilocarpine to act as sensitizer for ACh.

Our results are of interest in relation to the suggestion of Dale (1934) that pre-existing ACh, or an ACh-like substance, may be concerned normally in transmission through central synapses. In this connection we would offer the hypothesis that, in consequence of the stimulation or facilitation of synapses by eserine and ACh, streams of repetitive electrical impulses are initiated or accelerated across the synaptic junctions; these impulses lead to the discharge of the effector neurones.

Summary

1. The changes in the electrocorticogram in the cat and rabbit, induced by the local application of minimal amounts of 1 per cent eserine, $1:10^5$, 0.2–1 per cent acetylcholine (ACh) and 0.2 per cent atropine, were recorded by one or two cathode ray oscillographs.

2. Application to the cortex of 1 per cent eserine causes a reduction in amplitude of the slow waves and of the large fast waves; these changes indicate cortical stimulation, since they are associated with motor effects.

3. Application to the non-eserinized cortex of $1:10^5$–1 per cent ACh evokes potential changes comparable to, though weaker than, those from 1 per cent eserine. ACh in 0.2–1 per cent solution applied to the previously eserinized cortex evokes the Es-ACh spikes; associated motor effects show that the spikes indicate cortical stimulation. For the causation of these effects eserine must *precede* ACh, the reverse order being ineffective.

4. Atropinization of the animal precludes induction of the Es-ACh spikes and motor effects.

5. Pilocarpine locally is inert towards the electrocorticogram; further, it does not sensitize the cortex for ACh. The drug effects are not due to pH changes.

6. Eserine and ACh are believed to stimulate or facilitate synapses; eserine is a synaptic sensitizer for ACh. The synaptic action of eserine may be partly direct and partly due to its inhibition of cholinesterase, with lessened destruction of effective (natural) ACh. Potential changes from eserine are believed due to unequal stimulation of synapses with consequent

asynchronous firing of neurones. The Es-ACh spikes are believed due to powerful synaptic stimulation with synchronization of many neurones; the cells with short axons may be involved in this synchronization.

7. The hypothesis is proposed that, in consequence of stimulation of synapses by eserine and ACh, repetitive electrical impulses are initiated or accelerated across these junctions.

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CORD POTENTIALS IN SPINAL SHOCK

SINGLE VOLLEYS*

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INTRODUCTION

MUCH has been learned about the electrical activity of the spinal cord by recording from two leads on its surface (10, 11, 12, 13) from two leads on a dorsal or ventral root (1 and 2), from one lead on a root and one on the cord (4 and 1) and from one on two roots and one on an inactive point (25). So extensive is the activity, however, that further analysis requires a more restricted lead. One approach is by the use of microelectrodes, such as those employed by Umrath and Umrath on the cord (24) and by Forbes, Renshaw, and Rempel (6) on the hippocampus. Another is the study of potentials under conditions which limit the spread of activity. We have chosen the latter method and spinal shock as our tool. Or, to express the other aspect of a divided interest, we have employed cord potentials for the analysis of the more or less transient depression of reflexes induced by transection of the cord.

TECHNIQUE

Since our earlier work there have been several changes in technique. A better cathode ray oscillograph and a more efficient amplifier, for the design of which we are indebted to Dr. J. F. Toennies, have facilitated recording; a pair of thyrotrons and transformers proved useful for stimulation; and glass tubes with four silver electrodes in the form of loops have enabled us to lead off action potentials from nerves and roots. In most of our experiments exposure of the cord has been limited to two openings just large enough to permit slitting the dura and placing under it an electrode consisting of a silver disc of not over 2 mm. in diameter. Decerebrate cats and dogs, and young *Macaca mulatta* monkeys, ranging in weight from 3 to 4 kg., have been studied at various intervals after midthoracic section. The monkeys were not decerebrated but had a bilateral ablation of the motor and premotor cortex. Semitendinosus and quadriceps femoris were selected for myographic recording because they suffer less severely than do the muscles of the lower leg from the degenerative nerve changes which complicate reflex recovery in the spinal monkey (3 and 9).

Location of spinal shock. There is ample evidence connecting spinal shock with deprivation of innervation from the brain (20, 21, 22, 19, 7, 8, 9, 14, 15, 16, 17) but none has been offered to determine whether the block be at the internuncials or at the motoneurones. The first alternative should be associated with limitation of the internuncial potential; the second with reflex deficit out of proportion to such reduction. Since occlusion (10, 1), inhibition (12, 13, 2), and facilitation (13) have all been demonstrated in the potentials recorded from the dorsal surface of the cord, it is evident

* Aided by a grant from the National Committee for Mental Hygiene from funds granted by the Supreme Council Thirty-third Degree Scottish Rite Masons, for Research in Dementia Praecox.

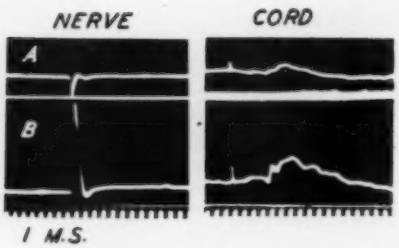

FIG. 1. Latency of cord potential. (A) threshold shock; (B) Maximal shock for A fibers of afferent nerve (sciatic). Note identity of latency. Monkey—6 hours after transection. 4/18/39.

that the potentials arise from a point of convergence. Since they are not affected by antidromic volleys into the motoneurones (11, 1), their internuncial origin is, in our opinion, firmly established. Further evidence of the post synaptic source of the cord potential is afforded by determination of its latency.

Synaptic Delay. The only experiments of which we are aware in which latency of transmission across a single set of synapses has been analysed, are those of Lorente de Nó (18) upon oculomotor neurones. In contrast to the results of Eccles and Sherrington (5) in the case of the flexor reflex, in which an unknown and possibly variable number of links are involved, Lorente de Nó found the value relatively constant and almost unaffected by the strength of the stimulus. Figure 1 illustrates a similar constancy and independence of the number of units involved in the latency of the intermediary potential of the cord. The total latent period is 4.07 msec. whether the stimulus be minimal or maximal for the A fibres of the peroneal nerve. The conduction rate determined from the time interval between stimulus artefact and nerve potential and the distance from cathode to active lead on the nerve is 75 meters per second; and the distance to the cord is about 225 mm. Hence only about 3 msec. are occupied in nerve conduction and about one must be attributed to synaptic delay. This estimate agrees with those in three monkeys in which dorsal roots were stimulated. These gave total latencies of 0.75, 1.56 and 1.66 msec. Of these three determinations only the first was in an acutely spinal animal before the onset of histologic changes in the internuncial perikarya. Such values afford additional support to the view that the potentials recorded from the dorsal surface of the cord arise in internuncial neurones.

FIG. 2. Cord potential with (A) both leads on cord; (B) Indifferent lead on denervated foot. Monkey 10 days after transection. 5/24/38. Note similarity in positive wave.

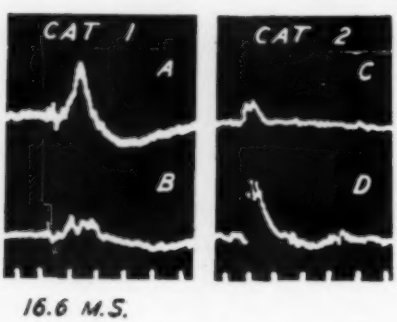

FIG. 3. Effect of transection on cord potentials of cat. (A) decerebrate; (B) 13 min. after transection. 7/20/37; (C) another cat, 6/17/37, 13 min. after transection; (D) 2 hr. later.

Effect of Transection Upon Cord Potentials

Barron and Matthews (1) observed no positivity when leading from dorsal roots in acutely spinal frogs, cats, and monkeys. They regard the positive wave seen when leading from the cord as the result of activity and hence of negativity at the level of the upper lead. We, too, have encountered diphasicity of this type and do not doubt that it is the correct interpretation

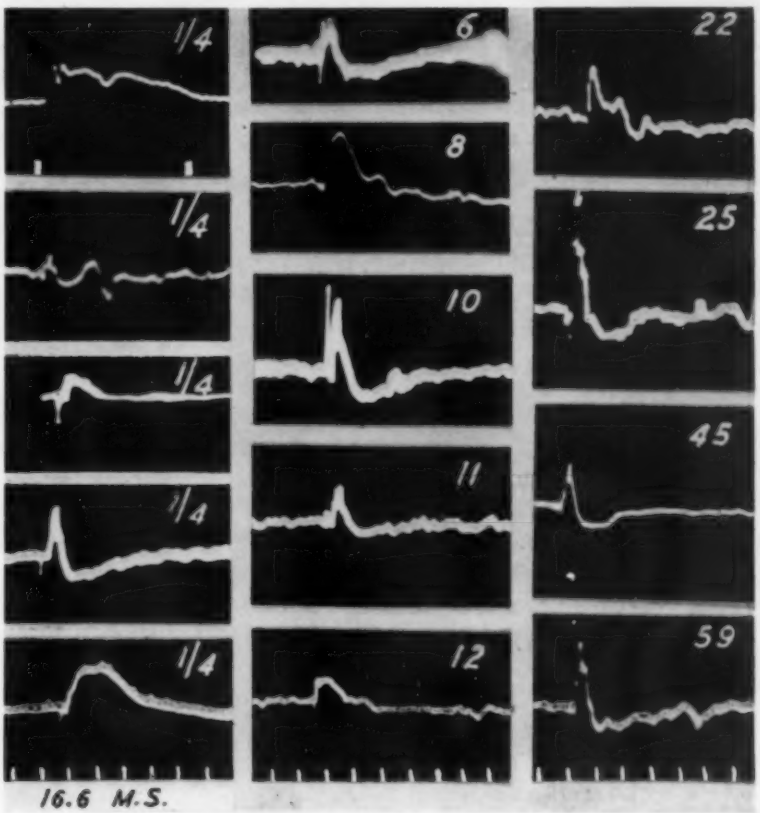

Fig. 4. Cord potentials in response to single volleys maximal for A fibers in 14 *Macaca mulatta* monkeys. Figures refer to interval between transection and recording in days. Note the increase in frequency and extent of positivity with chronicity.

of their data. On the other hand, experiments with the indifferent lead on the foot of a denervated limb have given records of positivity at the active lead indistinguishable from those obtained with the indifferent lead on the cord at the last thoracic or first lumbar level. Such records are shown in Fig. 2. These we regard as evidence of positivity developing within the cord. Because of their interest, experiments showing positivity have been the subject of much discussion. Yet, we cannot emphasize too strongly that when recorded immediately after transection, the animal which shows

positivity is the relatively rare exception. From our own records we can select twelve consecutive experiments on acutely spinal cats without a single case of positivity. In the chronically spinal animal, on the other hand, positivity is the rule. Figure 3 illustrates the extent of reduction of both negative and positive components induced by spinal transection in the decerebrate cat and the degree of recovery observed during the course of an acute experiment. Figure 4 illustrates cord potentials induced by single volleys just maximal for A fibres in the peroneal nerve in a series of monkeys at various intervals after transection. The increase in incidence and extent of positivity with chronicity is obvious.

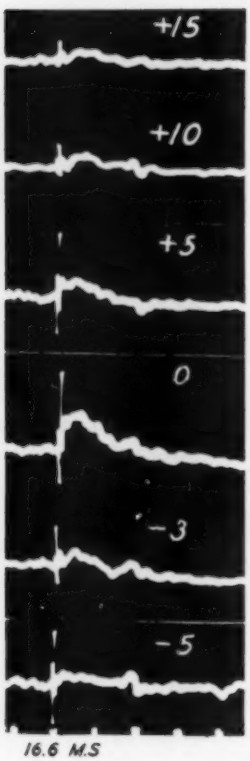

FIG. 5. Spread of cord potential in monkey 12 days after transection. Figures indicate distance in mm. of active lead above (+) and below (−) entrance zone of root stimulated. 2/16/39.

Limitation of region of internuncial activity

In the acutely spinal cat, Hughes and Gasser (11) traced the spread of the intermediary potential 30 mm. above and 10 mm. below the center of the root entrance zone. With this picture the acutely spinal monkey presents a striking contrast. We find that a shift of the lead of three to five millimeters above or below the optimal position may suffice to lose all trace of the potential. With increasing intervals after transection it extends further and further up and down the cord. Figure 5 shows the degree of spread 12 days after operation. Even at this stage of recovery, activity is demonstrable for only fifteen millimeters above and five millimeters below the optimal lead, or half the distance observed by Hughes and Gasser in the acutely spinal cat.

Thresholds. A roughly quantitative method of estimating the degree of shock at each part of the reflex arc is afforded by comparison of the thresholds for the spike potential of the afferent nerve, the intermediary cord potential, and the reflex response. This approach is limited by differences in adequacy of the two leads and by the restriction of myographic recording to a single muscle. We have recorded the cord potential at an amplification of 15 mm. per msec., the nerve potential at one of 3 mm. per msec. Presumably such thresholds represent the activity of several units.

In the cat and the dog transected under divinyl ether anaesthesia, from which recovery occurs a few seconds after withdrawal of the anaesthetic, the threshold of cord potential and reflex are usually identical and distinctly higher than that of the afferent nerve when first recorded. Both values fall progressively for about an hour when they closely approximate or equal that

recorded for the nerve. In this correspondence of threshold for nerve and cord we confirm the earlier result of Toennies (23, p. 380) on the cat. Here again, the monkey contrasts sharply with the cat and the dog. Figure 6 plots against days after transection the ratio of thresholds of potential of cord and afferent nerve and that of reflex and cord potential in a series of monkeys. The first value attains unity within six hours, the second not before twelve days and usually only after a considerably longer period. In the monkey reflex contraction of semitendinosus has never been encountered even to maximal stimulation in an acute experiment. On the other hand, if the lower extremities are left intact and stimuli are applied to a dorsal root, feeble flexion of digits or slight movement at the root of the tail have been observed at values that approximate threshold for nerve and cord in the acute preparation.

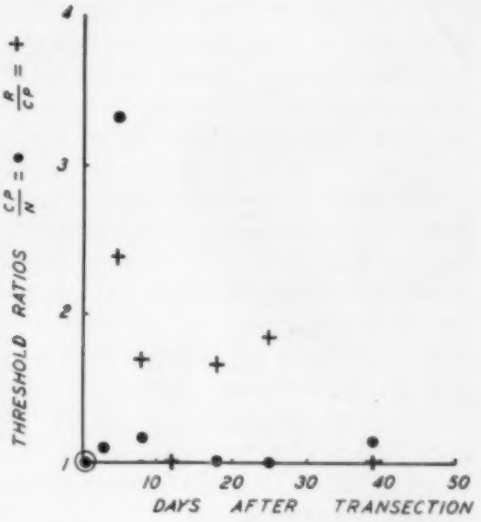

FIG. 6. Ratio of thresholds $\frac{\text{cord potential}}{\text{afferent nerve}}$ = black circles; $\frac{\text{reflex}}{\text{cord potential}}$ = Crosses; plotted against the interval after transection in days.

DISCUSSION

In the cat and the dog there is a period of about an hour after transection during which a minimal afferent volley fails to induce a cord potential. Yet any volley which yields a potential from the cord gives rise to a reflex response. To this rule occasional exceptions are found; but they are as apt to occur in chronic as in acute preparations and hence are probably due to factors other than spinal shock. Both cord potentials and reflexes, continue to change over a far longer period; yet at no interval after transection do they show a lack of parallelism. In these animals the only site at which we have demonstrated spinal shock is at the internuncial level. In the monkey, the restriction of the cord potential is far more severe; yet it appears to be less profound than the reflex depression. The evidence obtained from single volleys suggests that the gulf which separates the spinal monkey from the spinal cat and dog is due in large measure to shock to the motoneurones.

SUMMARY AND CONCLUSIONS

In cats, dogs, and monkeys cord potentials and reflex responses to single afferent volleys have been recorded at intervals after spinal transection ranging from a few seconds to two months.

The latency of the cord potential is independent of the strength of the stimulus and long enough to indicate an internuncial origin.

The effect of transection upon the cord potential is to reduce the amplitude and spread of the negative components and to abolish or almost abolish the positive components. These effects are far more severe and prolonged in the monkey than in the cat or the dog.

In the cat and the dog the threshold for cord potential and ipsilateral flexor reflex sampled in semitendinosus are equal and fall progressively during the first hour after transection at the end of which they approximate that of the afferent nerve. In the monkey, on the other hand, though the cord potential threshold approximates that of the nerve within six hours, the reflex threshold for semitendinosus requires twelve days or longer to attain that level. Reflex responses from this muscle have never been observed even to maximal stimulation in an acutely spinal monkey. On the other hand, stimulation of dorsal roots has given feeble toe flexion and slight tail movement at thresholds approximating those of cord potential and afferent nerve in an acute experiment.

Hence, in the cat and the dog, spinal shock has been demonstrated only at the internuncial level. In the monkey, on the other hand, in addition to more severe internuncial depression, there is evidence of deep and prolonged shock to the motoneurones.

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CORD POTENTIALS IN SPINAL SHOCK

MULTIPLE STIMULI*

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Recovery curves

IN EXPERIMENTS on cats with two volleys over the same afferent fibers Hughes and Gasser (2) correlated two types of recovery curve with characteristic features of the cord potential. When the potential contained only negative components, recovery was rapid enough to be limited solely by refractoriness; when a positive wave was recorded, it was associated with prolonged reflex unresponsiveness. Figure 1 illustrates the same relation in spinal monkeys. In the acute preparation positivity is almost absent and the cord potential from the second volley has recovered completely in 20 m.sec., a value which agrees well with that obtained by Lorente de Nó and Graham (5) in the case of oculomotor motoneurones in the cat. The presence of a potential of over forty per cent of the height of the control at even the shortest interval is presumably due to units facilitated by the first volley and discharged by the second as noted by Forbes, Querido, Whitaker and Hurxthal (1) in the case of reflex responses. In the chronic animal the positive wave is well developed and lasts almost to the end of the recovery curve. Depression of the second cord potential is profound and prolonged. At 20 m.sec. (the interval of complete recovery in the acute case) the second cord potential is only twenty per cent of the height of the control. This we regard as inhibition.

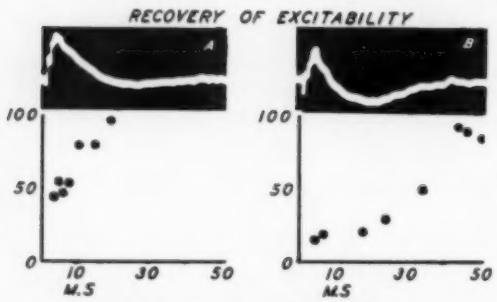

FIG. 1. Relationship of positivity to recovery of cord potential in the spinal monkey. (A) No positivity. Recovery in 20 msec. 6 hours after transection. (B) Positivity present. Recovery in 42 msec. 45 days after transection. 11/29/38–1/5/38.

Form of tetanic cord potential

Figure 2 illustrates the form of the tetanic potential in the afferent nerve and in the internuncial neurones of the cord, the former at an amplification of 3 mm. per mv, the latter at one of 15 mm. per m.sec. In the nerve

* Aided by a grant from the National Committee for Mental Hygiene from funds granted by the Supreme Council Thirty-third Degree Scottish Rite Masons, for Research in Dementia Praecox.

records this amplification is too low to demonstrate the positive after potential. In the response of the cord to a single volley the positive wave is obvious. At low frequencies, subsequent volleys giving negative waves that

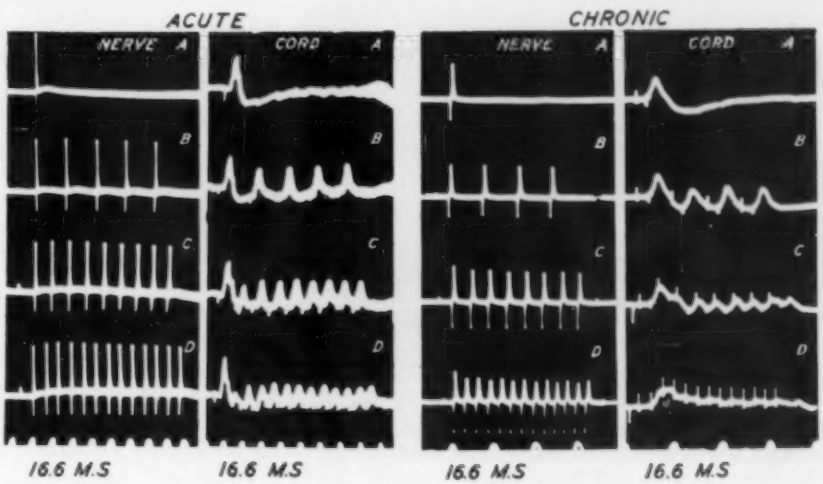

FIG. 2. Response of the acute (6 hours) and chronic (45 days) spinal monkey to stimulation of the peroneal nerve at varying frequencies. Stimuli maximal for A fibers. Rates per second: acute monkey (A) single volley (B) 26, (C) 68, (D) 94. Chronic monkey (A) single volley, (B) 77, (C) 142, (D) 232. 11/22/38–1/5/39.

are but slightly reduced, add little or nothing to the positivity ascribable to the first volley. As the frequency is increased within the range at which there is no reduction of spike height in the afferent, the second internuncial crest is severely cut and those which follow attain a height intermediate between it and the first crest. The positivity, though no deeper than that from a single volley, is prolonged to the end of the tetanus. Finally, at frequencies in which the afferent spikes are slightly reduced by relative refractoriness, the negative internuncial crests are greatly diminished in height, overlap each other, and obliterate any trace of positivity. A comparison of the internuncial responses to a single volley and to a tetanus of over two hundred per second presents a picture so different from the behavior of peripheral nerve as to suggest an origin from perikarya or dendrites. The virtual absence of positive wave at low frequencies in all responses after the first recalls the similar picture previously reported (3) in

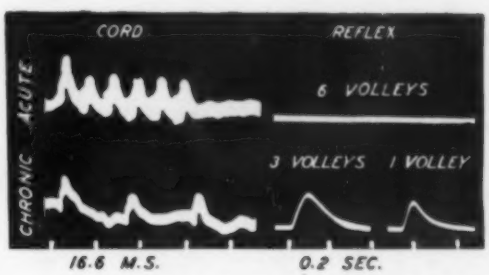

FIG. 3. Comparison of internuncial and reflex activity (semitendinosus) resulting from multiple volleys in the acute (6 hours) and the chronic (59 days) spinal monkey. Peroneal stimulation. 1/22/38–1/12/39.

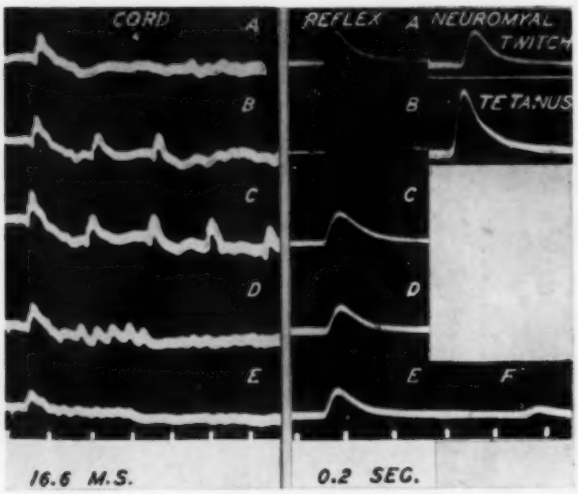

FIG. 4. Cord and reflex response (semitendinosus) in chronic spinal monkey (59 days). Peroneal stimulation (A) single volley, (B) 3 shocks, rate 40 per sec., (C) 5 shocks, 50 per sec., (D) 8 shocks, 150 per sec., (E) 10 shocks, 230 per sec., (F) reflex response to second period of stimulation 0.8 sec. after E. Stimuli maximal for A fibers. 1/12/39.

the case of crossed inhibition of a single volley and supports the view then advanced that negativity and positivity result from activity of different units.

Reflex shock

So far as the intermediary potentials are concerned, the effect of repetitive firing is similar in the acute and the chronic monkey as illustrated in Fig. 2. Figures 3 and 4 illustrate the contrast between the internuncial activity and the reflex depression. In the preceding paper it was stated that a reflex response of semitendinosus to a single volley in the monkey had never been observed. Similar silence in the face of repetitive stimulation is illustrated in Fig. 3. Even the chronic animal, which gives a large reflex to a single volley, suffers little addition to the response from subsequent volleys (Fig. 3 and 4). Such small reflex increments as these contribute are in inverse relation to the frequency of stimulation. The attribution of these results to the state of the muscle is eliminated by the neuromyal twitch tetanus ratio which contrasts sharply with the reflex picture (Fig. 4). In the reflex record at the bottom of Fig. 4, a second period of stimulation occurs 0.8 second after the first and yields a contraction of only 20 per cent of the tension of the preceding response. Thus, even two months after transection, when the single volley reflex is fully restored, it is elicited at the cost of prolonged succeeding depression. Whether this should be regarded as inhibition or fatigue is difficult to decide. Inhibition is usually observed in association with internuncial positivity and is roughly commensurate therewith in intensity and duration, though frequently outlasting the recorded electrical change. Here, on the contrary, little positivity is added to that from the initial volley, though negative waves are but slightly

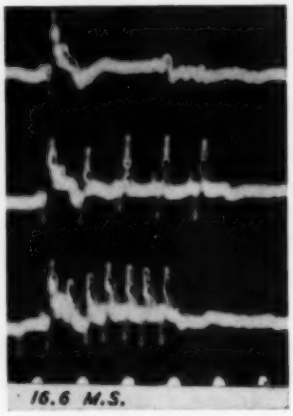

FIG. 5. Cord potentials of acute cat. 5/23/39.

reduced at frequencies yielding a tetanic tension scarcely exceeding that from a single stimulus. When it is recalled that in the cat tetanic stimulation gives an internuncial response indistinguishable from that of the monkey (Fig. 5), but a reflex tetanic tension twice that from a single volley (4), it is difficult to resist the conclusion that the difference in reflex response is due to differences in the state of the motoneurones rather than in the nerve impulses playing upon them. In so far as this opinion depends upon comparison of cat and monkey, however, it hinges upon the assumption that inhibition of the reflex may be measured at the internuncial level as accurately in the latter animal as in the former. So far as ipsilateral inhibition is concerned, this appears to be true (Fig. 6). Hence we incline to the view that in even the chronic spinal monkey there persists, at a point downstream from the internuncials whose activity is recorded, a significant degree of depression.

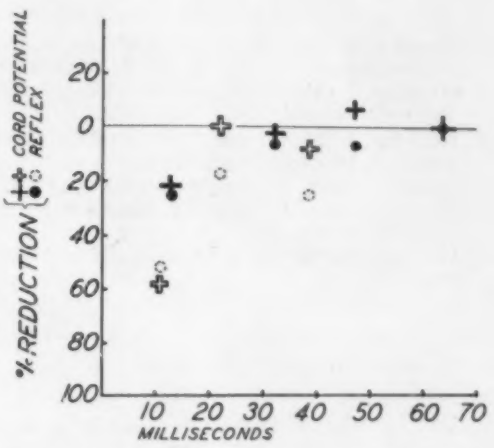

FIG. 6. Recovery curve of ipsilateral inhibition of flexor reflex (semitendinosus) and cord potentials. Data from 2 chronic monkeys. Circles refer to reflex, crosses to cord potential. Black symbols, monkey transected 25 days, 7/5/38; white symbols, monkeys transected 59 days, 1/12/39.

SUMMARY

In the spinal *Macaca mulatta* monkey, inhibition of the internuncial response to the second of two volleys to an afferent nerve is contingent upon the presence of a positive wave in the preceding cord potential. In the absence of such positivity, internuncial recovery from refractoriness is complete in 20 to 25 msec. Repetitive stimulation gives a series of internuncial potentials in which little positivity is added to that incident to the initial volley. Such a pattern contrasts sharply with that obtained from peripheral nerve and hence suggests a perikaryal origin and different units for the sources of negativity and positivity respectively.

The acutely spinal monkey gives no contraction of semitendinosus in response to afferent stimulation by either single or multiple volleys. The chronic monkey yields a large contraction to single volleys to which little is added by further stimulation even at frequencies at which the cord potentials are but slightly reduced. The view is advanced that in even the chronic monkey there persists a considerable degree of depression downstream from the internuncials recorded, presumably at the motoneurones.

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CORD POTENTIALS IN SPINAL SHOCK

CROSSED EFFECTS IN MONKEY, *MACACA MULATTA**

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INTRODUCTION

AMONG the latest reflexes to recover from spinal shock are those that depend upon the efficacy of internuncial neurones that cross from one side of the cord to the other. The localization of points of obstruction in these arcs consequently requires the use of chronically spinal animals whose cords have suffered as little deterioration as possible. So severe is the course of "isolation alteration" in the spinal monkey that only the exceptional preparation is suitable. Consequently, the data presented in this paper lack confirmation upon an extended series. Yet they impress us as sufficiently significant to justify our conclusions.

Recovery of crossed potential

By placing two alternative ground leads as far laterally as is consistent with contact with the dorsal columns it is possible in the acute monkey to demonstrate almost complete restriction of the cord potential to the side of stimulation (Fig. 1A). In an animal recorded twelve days after transection (B) the contralateral potential is still far smaller than the ipsilateral; but at fifty-nine days (C) the height is the same on both sides of the cord. Row D illustrates potentials from a monkey whose cord was hemisected on the right sixty-four days and transected three days before recording. Stimulation of a nerve of the acute side gives rise to a considerable ipsilateral and a brief contralateral potential. Stimulation on the chronic side presents a picture complicated by spread of activity to the upper lead which reduces the magnitude of the potential recorded from the chronic side and reverses the sign of the potential recorded from the crossed lead. The brevity of the negative potentials and apparent increase in contralateral positivity in the chronic spinal monkey (C) are presumably due to the same diphasic artefact. This is indicated by the records of the bottom row, E, taken from an acutely spinal cat with the grid lead on the foot of a denervated leg. Here the contralateral potential is virtually identical in size and form with the ipsilateral. Such prompt recovery in the cat contrasts sharply with the picture in the monkey even twelve days after transection. The positive wave in the cat potentials emphasizes a point insisted upon in the first paper of this series: that spinal positivity is by no means always a diphasic artefact.

* Aided by a grant from the National Committee for Mental Hygiene from funds granted by the Supreme Council Thirty-third Degree Scottish Rite Masons, for Research in Dementia Praecox.

To return to the recovery of the crossed cord potential; that of the contralateral side attains equality with the ipsilateral in a few hours in the cat, within two months in the monkey.

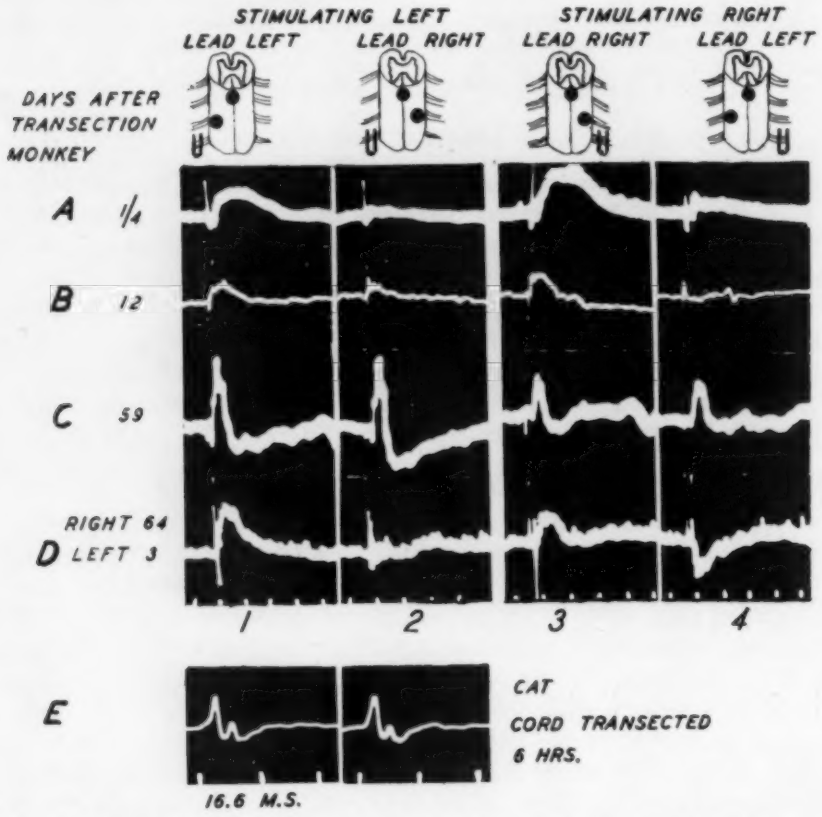

FIG. 1. Ipsilateral and crossed cord potentials recorded with lower lateral ground and upper medial grid lead at various intervals after spinal transection.

Column 1 Stimulus left, lead left.
Column 2 Stimulus left, lead right.
Column 3 Stimulus right, lead right.
Column 4 Stimulus right, lead left.
A, C, and E, stimuli to peroneal nerves.
B and D, Stimuli to 7th lumbar dorsal roots.
Note complete recovery of crossed potential in monkey (C) after 59 days, in cat (E) after 6 hours. A 11/29/38; B 2/16/39; C 1/12/39; D 2/7/39; E 5/23/39.

Source of crossed cord potential and site of its block. These questions may be advantageously approached by chronic hemisection followed by acute transection in the monkey. Records from such a preparation are shown in Fig. 2. Several of these are marred by artefacts from the electrocardiogram (the downward deflections in A2, B1 and 2, C2, and D1) which may be ignored. On stimulation of a dorsal root of the chronic side, there is a well

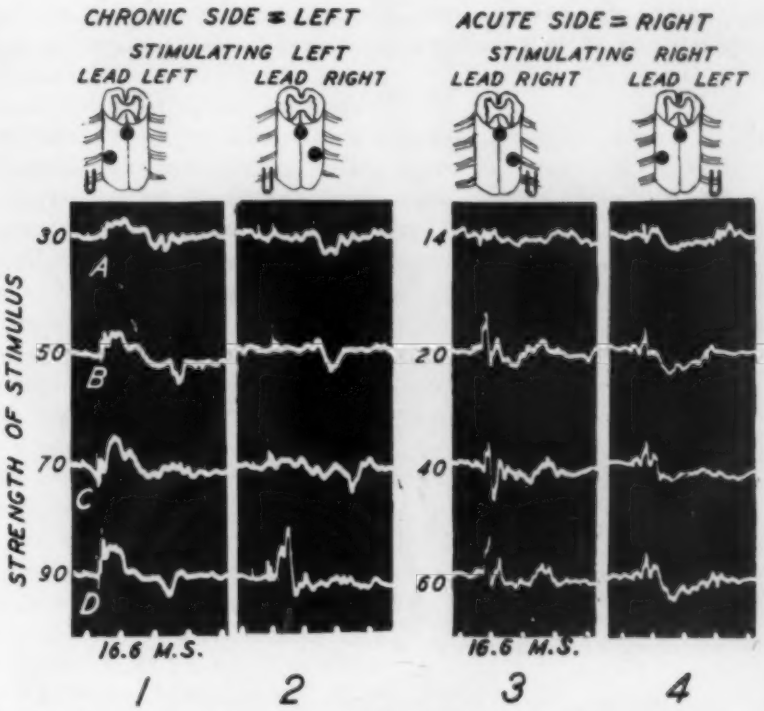

FIG. 2. Ipsilateral and crossed cord potentials recorded with lower lateral ground and upper medial grid lead in response to various strengths of stimulus to the 7th lumbar dorsal roots in a monkey hemisected on the left 39 days, transected 5 days before recording. Note the difference in threshold of the crossed potential of the two sides. Downward deflections in A2, B1 and 2, C2 and D1 are artefacts from the electrocardiogram. 3/7/39.

developed ipsilateral potential at a strength of 30 (arbitrary units) but no contralateral potential even at 70. At 90 a contralateral potential appears after a latency of 6.4 msec. or over 5.6 msec. longer than that on the side of stimulation. On the other hand, when a root of the acute side is stimulated, the potentials of both sides appear at the same threshold of 14 and with stronger stimulation the amplitude of the contralateral potential is not far short of that of the ipsilateral.

Since the thresholds for both potentials are the same in response to a root of the acute side, it is evident that when a root of the chronic side is stimulated, the crossing neurones must be transmitting impulses in response to stimulation far below

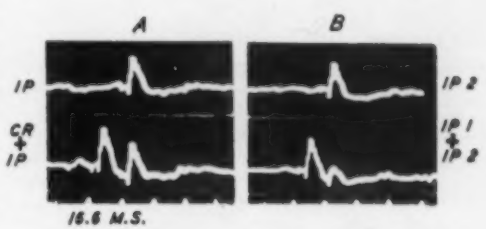

FIG. 3. Absence of crossed inhibition (A), contrasted with marked ipsilateral inhibition (B), of cord potential in a monkey 59 days after transection. Mid dorsal leads. Stimulation of peroneal nerves. 1/12/39.

threshold for the crossed potential. Since there is no reason we know of why the potentials of the crossing axones should not be as readily recorded as those of axones of the dorsal horn cells on which they terminate, we are forced to the conclusion that the contralateral cord potential is associated with activity of perikarya or dendrites sufficient in magnitude or duration to yield a far larger potential record than that due to spike potentials of axones in their vicinity. The same data lead to another conclusion: that the block of the crossed potential results from a raised threshold of the cells of the contralateral dorsal horn and not from lack of impulses playing upon them. Finally, they afford further conclusive evidence of the internuncial origin of cord potentials.

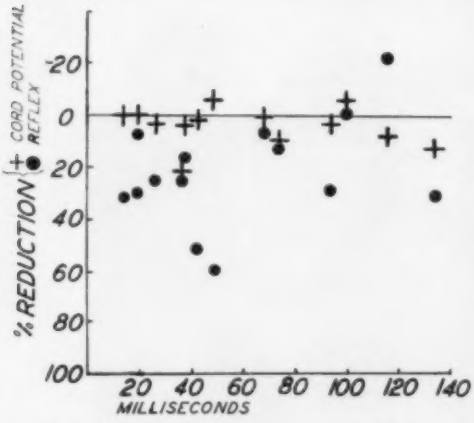

FIG. 4. Recovery curve of crossed inhibition of the flexor reflex (semitendinosus) in the chronic monkey recorded in Fig. 3. Note the frequent occurrence of reflex inhibition without reduction of the negative cord potential. Stimuli maximal for A fibers of peroneal nerves. 1/12/39.

Site of crossed inhibition of ipsilateral flexor reflex. Lorente de Nó (5), Hughes and Gasser (3), Hughes, McCouch and Stewart (4) and Bonnet and Bremer (2), have advanced evidence for the occurrence of inhibition at the internuncial level in the cat. Even in the cat, however, crossed inhibition of the ipsilateral flexor reflex is usually slightly more profound than that of its cord potential, although the corresponding recovery curves parallel each other to a remarkable degree (4, p. 413). In the monkey, we have recorded crossed inhibition in only a single animal, which had been transected fifty-nine days previously. The crossed cord potential was fully developed (Fig. 1C). Ipsilateral inhibition at the internuncial level was profound (Fig. 3). Crossed inhibition, though not sufficiently consistent to give a smooth curve (Fig. 4) was occasionally definite in the myographic record. Yet the corresponding cord potential developed to almost or quite the full height of the control (Fig. 5). Hence, in the monkey, crossed inhibition may occur down-

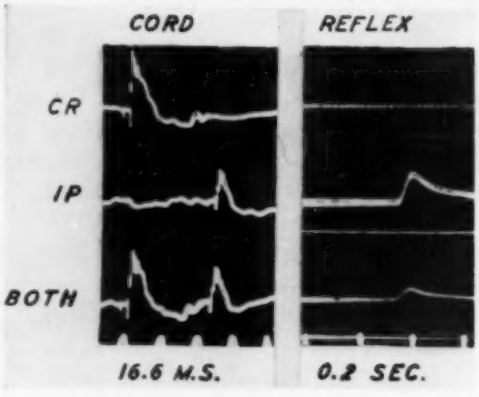

FIG. 5. An example of the contralateral reflex inhibition without reduction of cord potential plotted in Fig. 4. 1/12/39.

stream from the internuncials recorded by the cord potential, presumably at the motoneurones.

Summary

In the spinal Macaca mulatta monkey the contralateral component of the intermediary cord potential is scarcely detectable in the acute preparation, is small at 12 days after transection but has attained the magnitude of the ipsilateral component within two months.

In the chronically hemisected, acutely transected animal, the ipsilateral potential spreads farther up the cord when the stimulus is applied to afferents of the chronic side than when to those of the acute side. When the chronic side is stimulated, the threshold for the crossed cord potential is far higher and its latency far longer than that for the potential on the side of stimulation. When afferents of the acute side are stimulated, the thresholds for ipsilateral and contralateral potentials may be identical and the latter potential may approximate the magnitude of the former. From these data the following conclusions are drawn:

1. The contralateral cord potential is associated with the activity of perikarya or dendrites and not merely with that of axones.

2. Block of the crossed cord potential is due to a high threshold of the cells of the contralateral dorsal horn and not to lack of impulses playing upon them.

3. The above data yield evidence of the internuncial origin of the cord potential.

In the cat crossed inhibition of the internuncial potential parallels that of the flexor reflex, though usually it is somewhat less intense. In the chronic monkey, on the other hand, crossed inhibition of the reflex may occur without reduction of the corresponding cord potential. This indicates a locus of inhibition downstream from the internuncials recorded—presumably at the cells of the anterior horn.

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AN ATTEMPT TO PRODUCE SLEEP BY DIENCEPHALIC STIMULATION*

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CONSIDERATION of the literature indicates that at present there are two main theories of sleep, with many modifications of the parent theories. One theory proposes that sleep is a state of diminished activity of the brain and is a passive process; the other suggests that sleep is an active inhibition of the cortex and lower centers by a so-called "sleep center." Since electric currents can be used for either stimulation or destruction of living tissues by a proper choice of wave form and intensity, it seemed possible that stimulating or destructive electric currents could be used in the brain to obtain data bearing on the mechanism of sleep.

Many workers have used electric currents in experiments involving large areas of the nervous system, but few experimenters have attempted to investigate small areas where the site of action of the current was accurately known. Fewer still have controlled the experiments by preparing histological sections and examining the tissues for visible damage. Hermann (1885) placed marine animals in water through which a current was flowing and the animals aligned their bodies in the direction of current flow ("galvanotropism"). Scheminsky (1936) reported that when the alignment was such that the head was toward the anode the animal was very quiet or in a state of "electronarcosis." Scheminksy explained the depression as a state of anelectrotonus of cell bodies. However a state of electronarcosis has been produced with alternating currents in marine forms (Rosenberg, 1928, and Harreveld, 1937) and in mammals (Sack and Koch, 1933). Tschagowetz (1912) found that "galvanonarcosis" could be produced in cats by putting an anode on the head and a cathode on the sternum. Respiration and pulse rate were normal during the period of narcosis. The results with cats could not be repeated on dogs by Ivy and Barry (1932).

Direct current has been used locally in the brain by Marinesco, Sager and Kreindler (1929). Anodal polarization in the tubero-infundibular region facilitated sleep, whereas cathodal polarization caused excitement. The effective region was between the optic chiasma and mammillary bodies, between the junction of the thalamus and hypothalamus and between planes just lateral to the columns of the fornix on each side. Currents through the thalamus or caudate nucleus seemed to have no effect.

Electric stunning of animals has been performed by many workers with

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the type of current used by Leduc (1907). This was a unidirectional interrupted current with a square wave form at about 100 cycles per sec. and an interval to impulse ratio of 1 to 9. Leduc applied the current through external electrodes, the cathode being placed on the head of the animal and the anode in the midline of the back. The direction of current flow was opposite to that in the electronarcosis experiments of Scheminsky and others.

Pachon and Delmas-Marsalet (1924) employed a feeble galvanic current interrupted 20 to 30 times per sec. to stimulate the caudate nucleus of dogs in the waking state. Chewing, licking and swallowing movements and grimaces occurred, and at times there were circus movements to the side opposite the one stimulated. Somnolence was not produced; and if the animals were asleep they were awakened by such a stimulus. Hess (1932) advocated a unidirectional current interrupted 4 to 15 times per second with the rate of rise and fall of current retarded by self induction coils and condensers. During work on peripheral nerves, Hess found that use of a current of this type resulted in approximation of the thresholds for fibers in autonomic and somatic nerves, and therefore advocated its use in the interior of the brain. Hess used a unique method for orientating electrodes in the brain and checked the approximate position of the electrode tips after each experiment. His methods were an improvement over the free hand methods of previous workers, although they were probably not as accurate as is possible with the use of the Horsley-Clarke machine followed by microscopical control of every experiment.

The method of approach in the present experiments was to pass electric currents through localized regions in the brain of an unanesthetized animal. If stimulation of a point caused sleep, the results could be explained as stimulation of a "sleep center" which actively inhibited other parts of the brain. If, however, destruction of an area produced sleep it would indicate that a decrease in activity of the brain permitted sleep and that sleep was a passive process. In this latter case the region involved when functioning normally could be thought of as a "waking center."

METHODS

Cats were used in all experiments. Under ether anesthesia a Horsley-Clarke machine was attached to the animal's head, a threaded iron tube was screwed into a trephine hole in the skull and electrodes lowered into the brain. The electrodes and use of the Horsley-Clarke machine have already been described (Ranson, 1934). By means of a special electrode holder carried by the stereotaxic instrument, one to three pairs of electrodes could be inserted at a time. Usually one pair was used with an electrode 3 mm. on either side of the midline. When more than one pair was used, one pair was 1.5 to 3 mm. rostral to the other. The electrodes were cemented in place with dental investment compound. The Horsley-Clarke machine was then removed, the external parts of the electrodes were cut short and scraped, and ether anesthesia discontinued. The animal was injected with 50 cc. of physiological saline intraperitoneally and left for four to five hours to recover from the ether. The cat was next tested as to the state of its pupils, posture, respiration, response to pain, motor initiative, righting reactions, placing reactions, perseverance of positions, resistance to passive movements, gait and emotional expression in the presence of a barking dog in order that subsequent changes might be noted. Two 30 gauge silk covered wires about 4 feet long connected the electrodes to the current source and allowed the animal to move without restraint.

Four different current sources were used. The first was simply a battery, series resistor and milliammeter for steady direct current. The second was of the type used by Hess with a mercury interrupter, and coils and condensers to modify the rate of change of current. The wiring diagram was the same as Fig. 12b, page 23, of Hess' monograph (1932). The addition of inductors and condensers of high values permitted the retention of the interruption of current and depolarization as specified by Hess but allowed elimination of the stimulating factor. The capacitance could be made as high as 85 microfarads and the inductance as high as 69 henries. This was more than enough to prevent stimulation of any peripheral or central nervous structure that was tested. The third current source contained a mechanical interrupter and was arranged as shown in Fig. 1. The resistance of the slide wire was negligible compared to the resistance of the coils and tissues. The condenser was the same value as recommended by Hess and the total resistance of the air cored coils was nearly the same. Although we were unable to find out the inductance of his coils, we checked the wave form of the current with a cathode ray oscillograph and found it to correspond to that in his figures. Measurement of photographic records of the oscillographic trace revealed that the current reached 95 per cent of its full value in 16 msec. The interrupter was set so that current flowed for one-fifth of each cycle with 5 interruptions per sec. The fourth current source was a Harvard inductorium. The four sources gave us then a steady direct current for the production of lesions, an interrupted direct current for the production of lesions, an interrupted direct current for stimulation and a faradic current for stimulation.

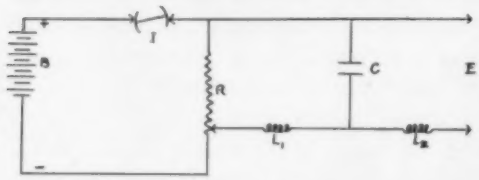

FIG. 1. Stimulating circuit. B, 12 volt battery; I, interrupter; R, 27 ohm slide wire; C, 4 microfarad condenser; L_1 and L_2, 1,700 ohm air cored coils; E, wires to milliammeter and animal.

In a typical experiment, an animal that had recovered from anesthesia was thoroughly tested. The current being used was then passed through the brain for 30 sec. unless some reaction occurred. After the current was turned off the animal was watched for delayed effects and then examined as to gait, posture, etc., just as at the start. The current was always weak at first and was gradually increased in subsequent 30 sec. periods until an intensity was reached that changed the behavior of the animal.

Immediately after the final observations, sometimes following the procedures described above and sometimes 12 to 24 hours later, the cat was anesthetized with ether, bled through the inferior vena cava and the brain injected with 10 per cent formalin through the carotid arteries. The electrodes were removed and the brain prepared for histological sectioning. The area of the brain penetrated by the electrodes was sectioned serially at 50 micra and every fourth section stained by the method of Weil. Adjacent sections were stained with cresyl violet. The relations of the electrodes to fiber tracts and nuclei and damage done to those structures were studied microscopically. An attempt was then made to correlate the physiological results of the experiments with the structures stimulated or destroyed.

RESULTS

The results obtained in our experiments permit division of the cats into five groups: (1) somnolent, (2) somnolent with a loss of motor initiative when awakened, (3) cataleptic, (4) excited and (5) negative. Cats that did not appear normal after operation and those in which histological study revealed incorrectly placed electrodes or damage to the brain were discarded. Fifty-four experiments were considered valid and will be reported here.

Somnolent cats. This group of seven cats includes only those which showed somnolence without exhibiting plasticity and loss of initiative when awakened. Animals displaying the latter signs, whether somnolent or not, were grouped with the cataleptic cats. Of these cats, three were treated

with steady direct current and four with a non-stimulating interrupted direct current. Somnolence was not produced by a stimulating current. A representative cat was number 35 which reacted as follows:

A non-stimulating interrupted direct current with a peak value of 0.4 mA. was applied for a total of one minute. The animal appeared to be somnolent but was awakened by slight pulling of hair over the abdomen and arose to an erect position. Ten minutes later the drowsiness had disappeared. Another minute of current caused the animal to go to sleep again in a normal position and this time the drowsiness lasted an hour. Throughout the somnolent period the animal could be easily awakened and when aroused demonstrated normal motor control and initiative, but if left alone would curl up and appear to sleep. The animal recovered from this last period of somnolence and seemed normal in every respect.

Microscopic examination of the brain disclosed that lesions had been produced at the tips of the electrodes (Fig. 2). The lesion on the left side was in the lateral hypothalamic area rostral to the mammillary nuclei. It lay between the anterior column of the fornix and the cerebral peduncle but damaged neither. The lateral hypothalamic area was markedly damaged, but the zona incerta, nucleus of the field of Forel and the subthalamic nucleus were spared. The lesion on the right side was also in the lateral hypothalamic area but spared cells rostrally and caudally. About half the fornix was demyelinated as was half of the mammillothalamic tract.

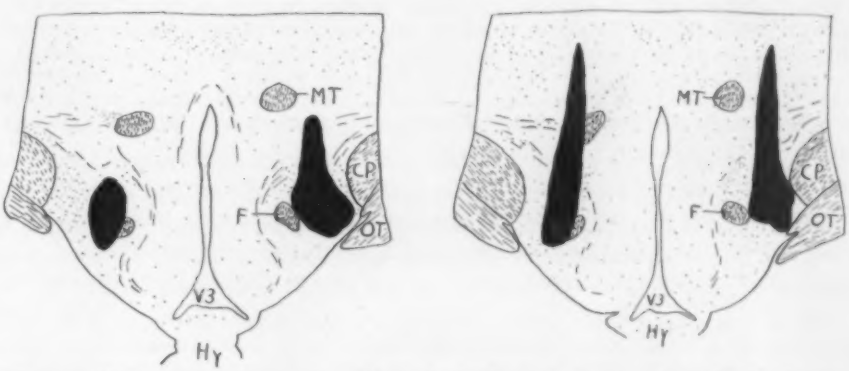

FIG. 2. Diagram of two sections through the hypothalamus of cat 35. Lesions are in solid black. F, Fornix; Hy, Hypophysis; CP, Cerebral Peduncle; OT, Optic Tract; SN, Substantia Nigra; V3, Third Ventricle; MT, Mammillothalamic Tract.

Five animals of this group had the tips of the electrodes placed bilaterally in the lateral hypothalamic area just rostral to the mammillary nuclei. Two had electrodes placed in the lateral group of nuclei of the thalamus, but the current required to produce somnolence was greater and of longer duration (*e.g.*, 3 mA. for 3 minutes in cat 4) and the degree and duration of the somnolence was less than in the hypothalamic experiments.

Cats with loss of motor initiative. Animals in this group exhibited somnolence and when awakened showed subnormal motor initiative. They would stand or lie for many minutes without initiating voluntary movements and responded with a minimum of movement to loud noises and handling. However, these cats could not be molded into abnormal positions as can be done with truly cataleptic cats.

Of the eight cats in this series, five had electrodes placed in the lateral hypothalamic area and three in the thalamus. The current used in two of the hypothalamic cats and all experiments on the thalamus was a steady direct current, the strength of which was about 1 mA. in the hypothalamic experiments and as high as 3 mA. in the thalamic experiments. The current used in the other hypothalamic experiments was a non-stimulating interrupted direct current with a peak value of 0.4 mA. Upon histological study, the damage found in the hypothalamic experiments was similar to that in the previous group. There was no constant difference in the lesions of the first two groups to explain the loss of initiative in one group and not the other. Cat 14 can be described as typical of the thalamic experiments.

Cat 14 was treated with a steady direct current of 3 mA. for 3 one minute periods before becoming drowsy but was definitely somnolent at the end of the fourth period. The animal was very easily aroused by noises or touching and reacted vigorously to pinching of its tail. Abnormal postures were quickly righted and there were no signs of plasticity. The gait was normal and righting reflexes were active, but placing reactions were absent. There seemed to be a loss of initiative as the cat would remain in one place if left alone, frequently going to sleep.

Examination of the brain disclosed extensive bilateral thalamic destruction. On the left side the lesion destroyed almost the entire lateral group of nuclei and extended from the level of the rostral border of the posterior commissure to the anterior group of thalamic nuclei. There was considerable damage to the lateral habenular nucleus, pulvinar, dorsomedial, nucleus, nucleus centralis lateralis and some to the paracentral nucleus. There was a little involvement of the nucleus ventralis pars anterior. The lesion on the right side was more laterally placed but had the same rostro-caudal extent as that on the left.

Cataleptic cats. This group includes seven cats that exhibited somnolence, plasticity and loss of motor initiative, and includes three cats with spasticity and loss of motor initiative which did not become somnolent. The signs were similar to those described by Ranson and Ingram (1932) for cats with retromammillary lesions. Examples of this group are cats 31 and 32.

Cat 31 was treated with a non-stimulating interrupted direct current of 0.4 mA. peak value for a total of 2 minutes. Slight somnolence was produced, but the most marked changes were the development of a high grade plasticity and a total loss of motor initiative. The cat was indifferent to handling and would maintain any position into which it was put. The lesions were bilateral in the lateral hypothalamic area dorsolateral to the mammillary nuclei as shown in Fig. 3.

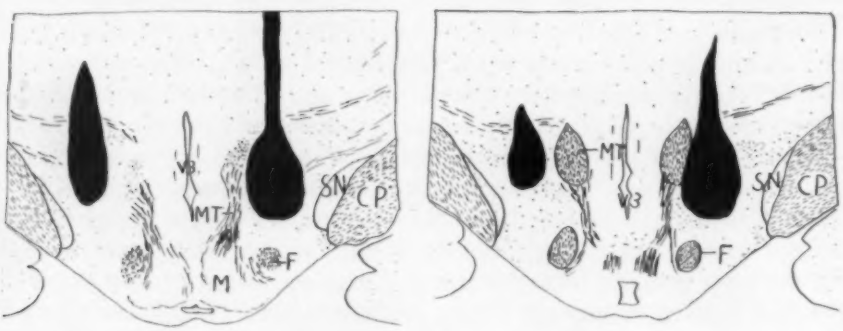

FIG. 3. Diagram of two sections through the hypothalamus of cat 31. Lesions are in solid black. Labels as in Fig. 2.

Cat 32 developed plasticity and loss of initiative but did not become somnolent. The type of current was similar to that of cat 31 but the lesions were a little more ventrally placed as is indicated in Fig. 4.

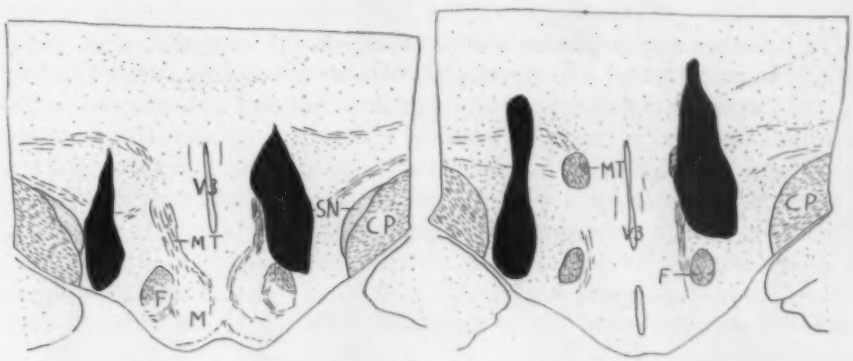

FIG. 4. Diagram of two sections through the hypothalamus of cat 32. Lesions are in solid black. Labels as in Fig. 2.

All 10 cats of the cataleptic group had lesions placed bilaterally in the lateral hypothalamic area and extending into the posterior hypothalamus. The current used in all of this group was of a destructive type. Plasticity and somnolence were not produced by a stimulating type of current.

Excited cats. Twenty-one cats treated with an interrupted stimulating direct current exhibited excitement, but none of them became somnolent. In many of the experiments faradic stimulation was carried out with little change in the type of response. Electrodes were placed in various parts of the thalamus, in nearly every part of the hypothalamus, the junction of the thalamus and hypothalamus and near the anterior commissure.

Stimulation of the hypothalamus in a waking animal resulted in responses previously described for the anesthetized animal, such as pupillodilation, respiratory changes, etc. In addition the cat usually became restless, walked around looking from side to side and cried softly, but rarely became markedly agitated if the current was kept low. Stimulation of the *thalamus* in the waking animal has been described by Kabat, Anson, Magoun and Ranson (1935) and Mussen (1934) so need not be repeated here. Lapping movements were produced by stimulation just ventral to the anterior commissure.

Negative cats. Eight cats reacted very little to passage of current through the brain. In four of these the heads of the caudate nuclei were destroyed bilaterally by a 3 mA. direct current. A transient drowsiness may have developed in one of these but could not be repeated. Cats 5 and 17 had very extensive destruction of the caudate nuclei following 9 minutes of a 3 mA. current with no signs of drowsiness, loss of initiative, plasticity, forced movements or loss of placing reactions. A destructive current was used in the hypothalamus of one cat and in the thalamus of two cats with little or

no response. Stimulation of the septum pellucidum in one cat and just ventral to the anterior commissure in two others yielded little of importance.

Discussion

The results indicate that when somnolence is produced by passage of an electric current through the diencephalon, the somnolence is due to destruction and depression and not to stimulation. None of the cats treated with a stimulating type of current became somnolent. Where the somnolence was transient, it can be assumed that the lesions seen microscopically were not solely responsible for the drowsiness. In the present experiments involving the hypothalamus, animals exhibiting slight or transient signs usually had small lesions. Other animals with lesions intentionally made large remained comatose until sacrificed. It is likely that animals with small visible lesions really had larger functional lesions at the time of deepest somnolence.

Electrostatic and electrolytic effects of currents can certainly depress nervous tissue even when not severe enough to produce histological changes. Any direct current of sufficient intensity to stimulate the interior of the brain will have a concomitant destructive action varying with the duration and intensity of the pulses. To decrease the rate of change of current with coils and condensers will increase the threshold of the tissues. A higher strength of current is then needed with its greater powers of depression. The argument that the effects of current spread can be eliminated by such a modified current has been discussed by Harrison, Magoun and Ranson (1938) and does not justify the use of such a current in the interior of the the brain.

Clinically the hypersomnia due to pathology of the diencephalon has been explained as evidence of a loss of function. Many cases of tumors involving or impinging on the hypothalamus have been reported and are usually associated with somnolence. Study of these cases leaves little basis for the explanation that somnolence is the result of an irritative phenomenon. In the present experiments somnolence was obtained by passing currents through the thalamus and hypothalamus. To produce drowsiness with electrodes in the thalamus, currents of long duration and fairly high intensity were required. When contrasted with the relatively short and weak currents used in the hypothalamus it leaves some doubt as to whether the current used in the thalamic experiments acted on the thalamus alone. From the very size of the thalamic lesions it is evident that the current was not local in action.

However, there is considerable support in the literature for the inclusion of the thalamus in any hypothesized sleep-waking mechanism. Trömner (1928) believes the thalamus is the only structure anatomically suited for a sleep center and suggests that it influences hypothalamic centers. Rowe (1935) discusses a cortico-thalamico-periventricular-hypothalamico-mesencephalic chain which when broken may result in sleep. Ranson (1939)

indicates that part of the hypothalamic drive to the cortex may be by way of the thalamus. Hirsch (1924) and Spiegel and Inaba (1927) give evidence that thalamic damage results in hypersomnia. Much of the action of the current in the present experiments must have been on the thalamus, but the high intensities used permit the criticism of current spread.

In the hypothalamus the visible lesions were in many cases small and discrete. Somnolence was easily produced when the electrodes were in the

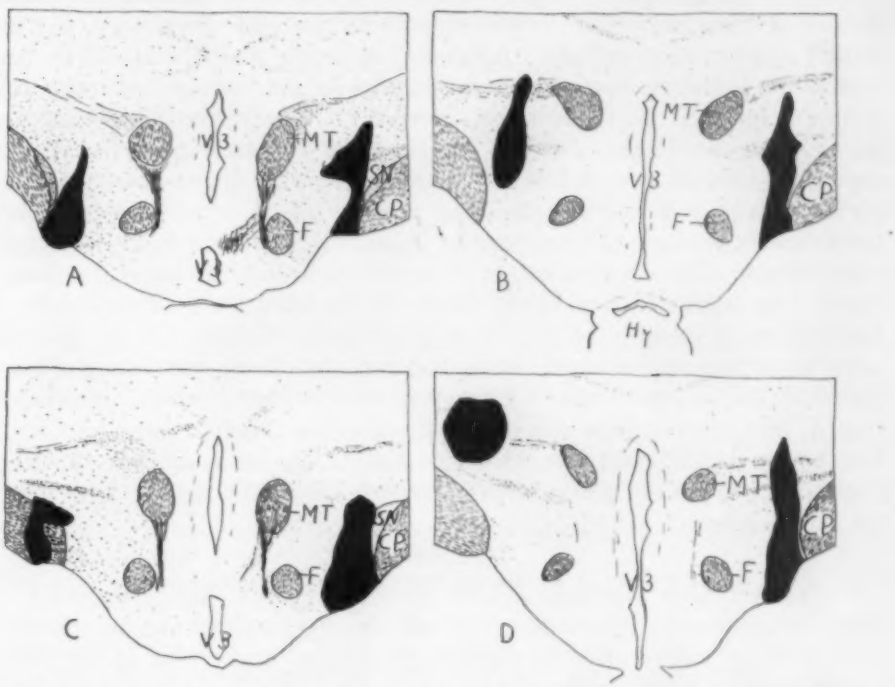

FIG. 5, A. and B, Drawings of two sections through the hypothalamus of cat 8 for comparison and C and D, drawings from sections of cat 10. Lesions are in solid black. Labels as in Fig. 2.

lateral hypothalamic area just rostral to the mammillary bodies. Lesions more medially and caudally placed were usually associated with catalepsy in addition to the somnolence. Difficulty in separation of the site of action of the current, however, is indicated by study of the brains of cats 8 and 10. The electrodes of these two cats were in very similar positions (Fig. 5); cat 8 became somnolent whereas cat 10 became cataleptic.

Stimulation of the various parts of the diencephalon from the posterior part to the anterior commissure resulted only in excitement and increased activity. Since Hess (1932) reported that in reality the microscopical controls in a large number of cases exhibited changes in the region of the stimulus, it is possible that his cases of somnolence may be explained by a temporary or permanent loss of function from electrostatic and electrolytic

effects. This view is shared by Serota (1939) who believes that sleep is associated with a decreased activity of the hypothalamus. Ranson (1939) gives evidence that the hypothalamus functions as a "waking center" when active, but when thrown out of function permits the decreased nervous activity characteristic of sleep. Kleitman in a long series of papers presents the view that sleep is a state of cerebral inactivity following a decrease of afferent impulses. His review (1929) discusses this problem.

Gagel (1936) reported a case of Foerster's in which mechanical stimulation of the posterior part of the hypothalamus produced sleep. Penfield's (1929) case of diencephalic autonomic epilepsy which was attributed to irritation, however, had signs of widespread autonomic discharge rather than somnolence. There seems on the whole to be a paucity of evidence supporting the theory that sleep is the result of an active process. The usual argument that sleep must be due to hyperactivity of the parasympathetic system because of the concomitant miosis, fall in blood pressure, fall in temperature, etc., is not necessarily valid. These are all signs of decreased sympathetic activity and are to be expected when the hypothalamus becomes less active during sleep. Some of the difficulties in explaining the mechanism of sleep have arisen because many workers fail to distinguish between processes leading to sleep and those resulting from sleep. Many of the so-called concomitants of sleep do not appear until after sleep has begun. The correct sequence of events has been studied by Kleitman and Doktorsky (1933) and by Cooperman (1936). Denny-Brown (1932) discusses the problem of active inhibition and states that there is little support for such a theory.

Summary

1. Destructive and stimulating electric currents were applied to the hypothalamus, thalamus, junction of the hypothalamus and thalamus, head of the caudate nucleus, septum pellucidum and region of the anterior commissure in waking cats.

2. Somnolence was produced by destructive action of currents when applied to the lateral hypothalamic area. Catalepsy tended to develop when the lesions involved the medial and caudal parts of the hypothalamus.

3. Somnolence was produced by destructive electric currents when applied to the lateral group of thalamic nuclei, but the strength and duration of the current was much greater than that in the hypothalamic experiments. It is possible that the effects were not solely thalamic.

4. Extensive lesions of the head of the caudate nucleus did not cause somnolence.

5. Stimulation of the structures mentioned above did not yield somnolence.

6. No evidence was obtained to support the theory that sleep is a phenomenon of active inhibition.

I wish to acknowledge the guidance, advice and helpful criticism of Dr. S. W. Ranson throughout the course of these experiments.

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RELAYED IMPULSES IN ASCENDING BRANCHES OF DORSAL ROOT FIBERS

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ONE of the most important questions in connection with the reflex discharge from the spinal cord by way of the dorsal roots is, what fibers carry the impulses? Certain facts only are known. On histological evidence the fibers must have their cells of origin in the dorsal root ganglia. Fibers conducting impulses at all the velocities characteristic for A fibers are involved (Toennies), and a large fraction of the dorsal root fibers are accessible to the discharge. For example, Toennies found that under special experimental conditions it was possible to cause about 35 per cent of the alpha fibers to be occupied by reflexly evoked impulses.

Additional evidence establishing the mediation of the dorsal root reflex by fibers originating from dorsal root ganglion cells will be brought forward in the present paper. Most, if not all, of the large afferent fibers, such as those which contribute to the first large elevation in the action potential of an afferent nerve, are known to divide soon after their entrance into the spinal cord into a short descending branch and a long ascending branch. Many of the ascending branches pass up the dorsal columns to end eventually in the nuclei of Goll and Burdach. Both branches send collaterals into the central grey matter of the spinal cord.

If fibers which divide in this way carry the reflex, it should follow that at the same time that the reflex discharge passes outward toward the periphery, impulses should also be conducted along the central branch toward the nuclei in the medulla.

METHOD

Cats were anesthetized with dial and the cord was exposed. The usual arrangement was to place stimulating electrodes on the sixth or the seventh lumbar dorsal root, and to lead the response by means of a needle electrode placed in the homolateral dorsal column some distance cranial to the site of entrance of the root stimulated. The differential input circuit described by Toennies (1938b) was employed. One of the grids of the input amplifier was connected to the needle electrode, and the other to the adjacent vertebra or muscle. After the electrodes had been put into place, the cord surface was flooded with paraffin oil to prevent drying. Measurements of the rectal temperatures were made, and in about one-half of the experiments the cord temperature was determined with a thermocouple designed for the purpose.

RESULTS

Form of the response in the cord. In the experiment illustrated in Fig. 1, the needle lead was placed in the dorsal column a few tenths of a millimeter below the surface and 13 cm. above the point of entrance of the stimulated

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dorsal root (L 7). When a single afferent volley was initiated by a shock applied to the root, the potential picture shown in the first record of Fig. 1 was obtained. The form of the response is characteristic. The action potential starts with a sharp spike-like elevation and is continued 2.9 msec. later by a second and more prolonged elevation. It can easily be shown that the first spike is the record of the impulses passing directly upward along the central branches of the primary neurons; and no comment need be made about it, beyond calling attention to the amount of the temporal dispersion of the impulses that has been occasioned by the long distance of conduction. The interest centers around the second elevation. If it is to be demonstrated as representing the centrally directed counterpart of the reflex discharge to the periphery, it must be proven to have properties in common with the latter. Experiments were designed to test these properties and their outcome is described in the following paragraphs.

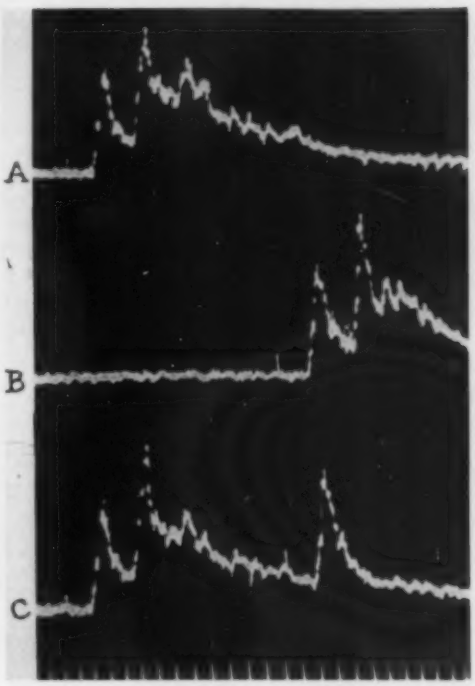

FIG. 1. Response in the homolateral dorsal column to a stimulus applied to the seventh lumbar dorsal root. Record C was obtained when the responses to single shocks as shown in records A and B were elicited during the same sweep. The needle lead was 13 cm. cranial to the entrance of the stimulated root. Rectal temperature, 36°C. Time in msec.

Relaying of the impulses. Without proof at the outset that the impulses originate from activity set up in the grey matter of the cord, there would be no occasion to inquire further. This proof, however, can be obtained in a simple manner. Toennies demonstrated that the reflex is readily inhibited by previous activity. From this observation it should follow that the starting of impulses along the tracts in the dorsal columns should be inhibited in a parallel fashion.

Record C in Fig. 1 shows the effect on the response of an afferent volley produced by the response of a similar afferent volley 13 msec. earlier. The nature of the effect can best be understood by comparing the conditioned response with the control isolated response in record B, immediately above it. All the second elevation has disappeared, leaving in pure form the spike-like potential derived from the ascending primary impulses. Thus, like the reflex impulses in the roots, the second elevation is inhibited. And as the time course of the inhibition is the same in the two, the presumption

is strong that the two are produced in the cord in the same way.

Localization of the response in the dorsal columns. The second point requiring proof was that the second elevation actually represents impulses passing through the dorsal columns. In order to test this point, systematic explorations were made of the regions in the cross-section of the cord from which the response could be led. The cord was examined with the aid of a needle electrode attached to a calibrated microdrive permitting insertion of the needle into the cord at any latitude or depth. Various cord levels were examined in this way, and in every experiment it was found that the potential could be picked up from the homolateral dorsal column; but that as soon as the needle penetrated below the column or crossed the midline, the potential disappeared.

Furthermore it was possible to make out considerable localization within the column, despite whatever lack of precision there may be in the power of the needle leads to localize responses. In the experiment illustrated in Fig. 2 the seventh lumbar dorsal root was stimulated, and a section of the cord was explored 8 cm. cranial to the root entrance. At the conclusion of the experiment the part of the cord from which the potentials had been led was fixed in 10 per cent formalin. Serial sections were subsequently cut, and examined to check the depth and position of the needle tracks. In the figure the positions of the needle at which the potential records were taken are marked on a microphotograph of an adjoining section.

It is clear from Fig. 2 that there is considerable variation at the several positions in the size of the potentials recorded, both with respect to the primary spike and the relayed discharge. A careful examination of the records brings out the fact that the maximum of the activity is along a diagonal line starting laterally at the surface in the region of position 2a and passing medially and ventrally between 2b and 3b, and between 2c and 3c toward 3d. Deep in the white matter the potentials tend to disappear, and near the midline they are very small. The finding thus is nicely in accord with what is known from degeneration experiments about the position of the central projections of the fibers of a dorsal root in the dorsal columns.

A point of greater significance that is brought out in the records of Fig. 2 is the close correspondence as to size between the primary spike and the relayed discharge. The fibers that carry the discharge must have the same position in the columns as do the fibers that carry the primary impulses from the roots. Just as the dorsal root reflex is largest in the fibers of the root which produced it (Toennies, 1938a), the relayed discharge is largest in the tract of the dorsal columns which carries the central projections of the root fibers evoking the discharge.

Latency of the relayed discharge. If the relayed discharge is conducted through branches of the dorsal root fibers that carry the reflex, the latencies of the two events—attributable to the sum of the synapse times in the grey matter of the cord—should be the same. The latency of the second elevation in the record presented in Fig. 1 was 2.9 msec. No figures on the normal

synapse time of the reflex were available for comparison, inasmuch as Toennies' figure of 4 msec. was obtained on preparations at a subnormal temperature. In order to supply the information, experiments were undertaken on decerebrated cats in which the cord temperature was maintained at 38.5°C. Stimulating electrodes were placed on one fasciculus of the seventh lumbar

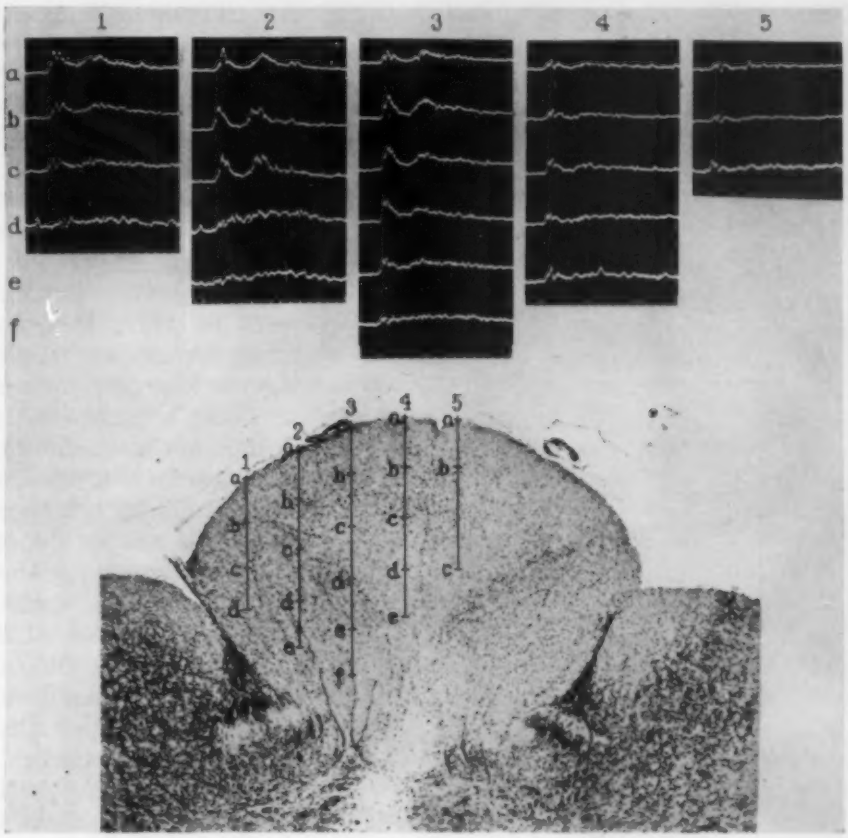

FIG. 2. Localization of the response in the dorsal columns. Stimulus applied to the seventh lumbar dorsal root. The needle leads were 8 cm. cranial to the root at the positions in the dorsal column marked on the microphotograph of an adjacent cord section. Rectal temperature, 36°C. Time in msec.

dorsal root, and the recording electrodes on another branch of the same root. After correction for root conduction, the reflex times were found to vary between 2.1 and 2.6 msec. The latency of 2.9 msec. for the second elevation in Fig. 1 is thus somewhat outside of the normal range for the reflex; but it was a proper value for the reflex in that particular experiment, as the cord temperature was about 35°C.

Conduction velocity of the relayed discharge. If the relayed discharge is

conducted through the ascending branches of the primary fibers, the velocity of conduction should be the same as that of the primary impulses, subject to the one reservation that if a single fiber carries both sets of impulses, the conductivity must have had time to return to normal between the primary and the secondary occupation. As a corollary of this line of reasoning it should follow that the second elevation should succeed the primary spike by an interval that is independent of the level of the cord at which the interval is determined.

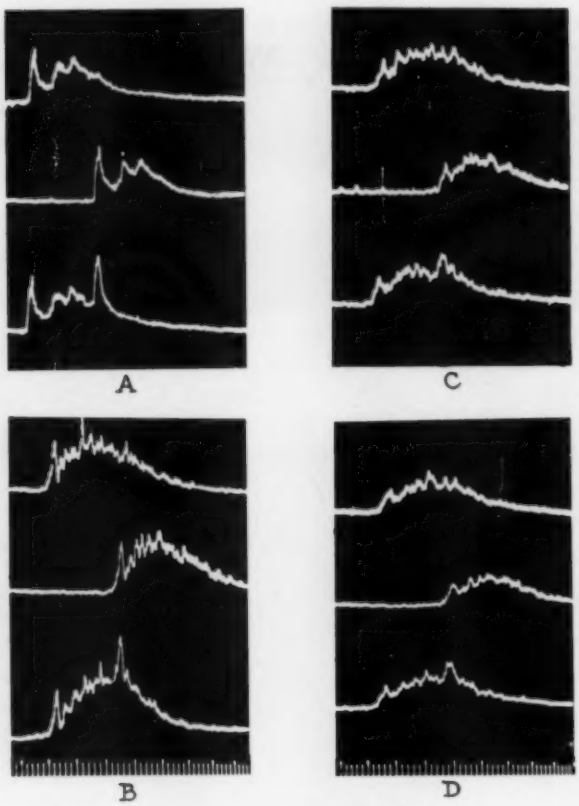

FIG. 3. Action potentials in the dorsal column at four distances of conduction. The stimulus was applied to the seventh lumbar dorsal root, and leads were made with a needle electrode placed successively at various distances cranial to the point of entrance of the root: 5.2 cm., record A; 14.3 cm., record B; 16 cm., record C; 18 cm., record D. Rectal temperature, 32.5°C. Cord temperature, 31.5°C. Time in msec.

Experimentation has shown that the interval is constant within the range of experimental error. Figure 3 shows the records from an experiment in which leads were taken at four distances from the root. In order to aid in the identification of the time of start of the second elevation, records were also taken of the primary spike stripped of the relayed impulses which overtake its slower components. The isolation of the spike was accomplished through inhibition of the relayed impulses by a previous response (lower records). When isolated, the spike reveals the base line from which the potentials of the relayed responses rise.

The intervals between the start of the spike and the start of the second elevation were found in the records of Fig. 3 to be the following: After 5.2 cm. of conduction, 3 msec.; after 14.3 cm., 3.5 msec.; after 16 cm., 3.0 msec.; and after 18 cm., 2.8 msec. The constancy of the periods indicates that the fastest of the relayed impulses must have the same velocity as the fastest of the directly conducted impulses. At the same time, the fact that the intervals did not get longer as conduction proceeded served to eliminate the possibility that the impulses at the start of the sec-

ond elevation might be carried upward in a series of short relays through the fasciculus proprius. The negation of the latter possibility is in accord with the findings in the localization experiments previously cited, as the maximum of the potential was found to be at a distance from the position of the fibers of the fasciculus.

Stimulation of the ascending branches of the dorsal root fibers. Thus far it has been shown that the second elevation in the action potential, recorded from the dorsal columns following the entrance of a single afferent volley into the cord by one of the dorsal roots, is attributable to impulses that have been relayed in the grey matter of the spinal cord and are passing up in the columns toward the medulla without further relay and at a velocity corresponding to that of the primary volley. It now remains to be shown that the impulses are actually conducted in branches of the fibers which carry the dorsal root reflex.

For descriptive purposes the dorsal root fibers may be divided into reflex-producing and reflex-carrying fibers, without prejudice as to whether the two groups are the same or different. A shock applied to the dorsal columns would stimulate the ascending branches of the two groups indiscriminately, and impulses would pass backward over the branches to the bifurcation of the root fibers, and then outward over the roots. At the same time by way of the collaterals into the grey matter of the cord, dorsal root reflexes would be produced, and relayed discharges would be dispatched cranially along the dorsal columns. If the pathways for the latter are the central branches of the reflex-carrying fibers in the roots, the impulses should meet and block any descending impulses in those fibers set up by a second shock applied to the columns; and there would then be a deficit in the number of impulses conducted over the dorsal root fibers, as compared with the number conducted after a control first shock.

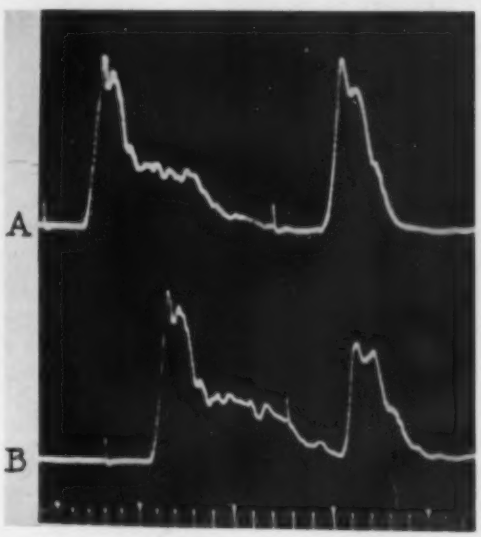

FIG. 4. The response led from the seventh lumbar dorsal root when two stimulating shocks were applied to the homolateral dorsal column 18.5 cm. cranial to the root. The intervals between the shocks were 12.9 msec. (record A) and 9.7 msec. (record B). Rectal temperature, 35°C. Cord temperature, 33.5°C. Time in msec.

After stating in advance that the impulses are blocked, as the theory demands, the evidence will be presented in terms of a specific experiment, illustrated in Fig. 4 and 5. Leads were placed on the seventh lumbar root,

with the ground electrode between the cord and the two grid leads, and the root was crushed near the distal grid lead. The stimulating electrodes, which were two small needles separated by 2 mm. and insulated except at the tips, were placed in the dorsal column near the midline, 18.5 cm. cranial to the root.

Two records taken at shock intervals of 12.9 and 9.7 msec. are shown respectively in records A and B of Fig. 4. In both records the first elevation starts with the directly conducted impulses and is continued by the reflex discharge, while the second elevation contains only the directly conducted impulses set up by the second shock, as the reflex at this time is inhibited. At the longer interval, 12.9 msec., there is no decrease in the height of the second response; but at the shorter interval, 9.7 msec., the height has been reduced 32 per cent.

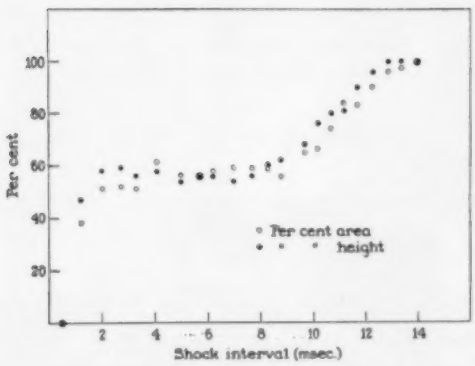

FIG. 5. The percentage decreases in the heights and in the areas of the action-potentials of the impulses set up by a shock applied to the dorsal column and conducted directly to the seventh dorsal root. The decreases are conditioned by the activity set up by a shock preceding the test shock by various intervals. Stimulus and leads as in Fig. 4.

A summary of the findings for stimulation intervals up to 14 msec. is presented in Fig. 5. The data are given in two ways: The percentage reductions in the heights and in the areas of the responses, as compared with the values at 14 msec.,—at which time the heights had fully recovered. The areas fall off somewhat more rapidly than do the heights, because the area method of measurement takes fuller account of the slowly conducted impulses that contribute to the tail of the action potential. Between 14 msec. and about 9 msec. the responses decrease progressively. Then they reach a plateau which is maintained until about 2 msec., at which time the responses begin to decrease rapidly.

The explanation of the course taken by the curve is the following. The shortest conduction time between the stimulating electrodes and the root was 2.3 msec., and about 3 msec. would elapse before the first relayed responses would start to pass upward along the column fibers. The impulses ascending from the root level would require a minimum of 2.3 msec. to get back to the locus of the stimulating electrode, and a minimal refractory period of 1.2 msec. (by test) would need to elapse after their arrival before the fibers could be stimulated. The sum of these times is 8.8 msec.

At times longer than 8.8 msec. the fibers having conduction velocities slower than the maximum are blocked. At 8.8 msec. the blockade reaches a maximum, and a shortening of the interval thereafter succeeds only in altering the point along the fiber path at which occlusion takes place. The

final decrease at very short intervals is occasioned by the refractory period of the column fibers at the stimulating electrodes, following the first stimulus.

Discussion

The sum of the evidence now available indicates that an afferent volley, whether artificially excited or made up of physiologically selected sensory impulses (Toennies, 1939), after a central reflex time of 2.1 to 2.6 msec. evokes a reflex in dorsal root fibers. At the same time that the reflex discharge passes outward to the periphery, the discharge is also carried along the central branches of the dorsal root fibers mediating the reflex toward the nuclei of Goll and Burdach. The centrally directed impulses are conducted along the dorsal columns at the same maximal velocity as that of the directly conducted sensory impulses; and for a given root they occupy the same band of fibers in the dorsal columns as do the sensory impulses. There is no fact that sets off the reflex-carrying dorsal root fibers from those conducting sensory messages. On the other hand, all the facts would be accounted for by the postulate of two fiber systems having similar properties, one system carrying sensory impulses and exciting the reflex, and the other discharging reflex impulses to the periphery and centrally directed impulses toward the nuclei in the medulla. Toennies (1939) has recently shown that the reflexly discharged impulses are able to condition the setting up of sensory impulses at the terminals of sensory fibers. But here again the experiments are susceptible of two interpretations,—an effect on the endings resulting from involvement of the fibers in the reflex, or a modification of the terminals through a postulated but unidentified set of special fibers not carrying sensory impulses. For the second alternative to hold, however, an added reservation has to be made as the result of the findings reported in the present paper. As the reflex-carrying fibers conduct impulses toward the medulla, the expectation would be that they would produce some effect there. If the anticipated effect exists, the only way in which the reflex-carrying fibers could fail to give account of conditions in the periphery would be for their peripheral terminations to be inexcitable.

Conclusion

At the same time that a reflexly evoked discharge of impulses passes over dorsal root fibers to the periphery, the impulses are also conducted along the ascending branches of these fibers in the dorsal columns of the spinal cord toward the nuclei in the medulla.

Summary

This investigation was designed to describe in further detail the properties of the dorsal root reflex response recently reported by Toennies. Since the dorsal root fibers divide and send long branches up the dorsal columns to the nuclei of Goll and Burdach, it should follow that simultaneous with the passage of the reflex response outward toward the periphery, a relayed

impulse should likewise pass up the dorsal columns. Cats were anesthetized with dial and the cord was exposed. Stimulating electrodes were placed on the sixth or seventh lumbar dorsal root, and a recording needle electrode was placed in the homolateral dorsal column some distance cranial to the site of the stimulated root. In accord with the expectation a relayed response was recorded following the direct afferent volley. The properties of the relayed response were found to be similar to the properties of the dorsal root reflex. Evidence was accumulated to show that the relayed response was carried by the ascending branches of the dorsal root fibers.

The author takes pleasure in expressing his gratitude to Doctor Gasser for encouragement and advice in the pursuit of this work.

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OBSERVATIONS UPON DIAPHRAGMATIC SENSATION*

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(Received for publication October 18, 1939)

THE phrenic nerve has been of interest to the embryologist, physiologist and surgeon mainly because it supplies a somatic motor innervation to the striated muscle in the diaphragm. The significance of the sensory components of the phrenic nerve was appreciated by Bourgery (1845) and Luschka (1853 and 1863), who was aware of shoulder-tip reference on stimulation of receptors in the phrenic distribution. Among others, Schreiber (1883) observed increases in blood pressure on stimulation of the central end of the cut phrenic nerve in the dog. Greene (1935) reported that dilatation of coronary blood vessels occurred subsequent to stimulation of the central end of the cut phrenic. Likewise, Thornton (1937) found that the phrenic nerve provides at least one afferent path for reflex broncho-dilatation, the efferent path of which is in the vagus. Little and McSwiney (1938) have used the pupillo-dilator reflex as an index of afferent impulses. In the cat, they found that the afferent fibers in the phrenic nerves enter via the dorsal roots of the 5th and 6th cervical segments and form the main pathway for sensory impulses from the diaphragm. Hinsey, Hare and Phillips (1939) degenerated the somatic motor and sympathetic fibers in the phrenic nerve of the cat and demonstrated histologically that this nerve contains myelinated sensory fibers of different sizes and unmyelinated ones.

That stimulation or irritation of the central portion of the diaphragmatic pleura or peritoneum may cause a pain which is referred into the shoulder-tip area is a well-recognized clinical phenomenon in man (Luschka 1863, Ross 1888, Felix 1922, Capps and Coleman 1932, Morley 1931, Woollard, Roberts and Carmichael 1932). This type of reference has been given a number of explanations, one of which was put to test in the experimental animal by Pollock and Davis (1935). Their work indicated to them that viscero-cutaneous reflexes caused changes in the environment of the skin in the shoulder-tip area. This vasomotor or chemical process was thought to be the result of impulses in sympathetic fibers and in turn to be the cause of stimulation of somatic receptors in the area, thus explaining the reference. However, in 7 of their cases after bilateral removal of the stellate ganglia, pain persisted when the diaphragmatic peritoneum was faradically stimulated. The explanation given was that some connection with the cord still existed. These experiments seemed inconclusive. In the light of the

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importance which has been attached to them, we have repeated certain phases of them and performed additional experiments.

METHOD

A study was made of nociceptive sensation in the central portion of the diaphragmatic peritoneum of cats and dogs. The spinal cord was completely transected at T4 or higher in all experiments. By breaking ascending conduction from levels below the section, conscious appreciation of sensation from the rim of the diaphragm was not present because this portion receives a sensory innervation from the lower intercostal nerves. Section of the spinal cord at C7 would not only serve to break ascending conduction but would also interrupt descending conduction for the activation of preganglionic neurons in the upper thoracic segments. After the spinal cord had been transected, a midline incision was made through the anterior body wall from the xiphoid process caudally about 8 to 10 cm., from which point the incision was extended laterally at right angles on both sides. By proper retraction of the rostral 2 flaps of body wall, it was possible to expose the abdominal surface of the diaphragm and apply to it bipolar faradic stimulation of rather high intensities (Harvard inductorium, 1 dry cell, coil separation 6–8 cm.). Consciousness of nociceptive stimulation in the lightly anesthetized or unanesthetized animals was indicated by vocalization, protrusion of claws, movements of the vibrissae, dilatation of the pupils, hyperpnea, and struggling. In our experiments, the pupils dilated when the diaphragm was stimulated after all possible thoracolumbar sympathetic pathways to them were interrupted, *i.e.*, transection of spinal cord at C7 or bilateral removal of sympathetic chains from above superior cervical ganglia to below the 7th thoracic chain ganglia. These were demonstrations of the significance of inhibition of the parasympathetic innervation in the dilatation of the pupil occurring subsequent to nociceptive stimulation (See Ury and Gellhorn, 1939).

At the termination of each experiment, a careful autopsy was performed to control the operative procedures.

OBSERVATIONS

Faradic stimulation of the central portion of the diaphragm induced consciousness of nociceptive sensation in all cases after the following experimental procedures were carried out:

1. The vagi and sympathetic trunks were sectioned bilaterally in the neck below the superior cervical sympathetic ganglion and the spinal cord was transected at C7 (four cats). Observations were made within 24 hours.

2. The right and left sympathetic chains were removed from above the stellate through T7 and the spinal cord was transected at T4 (1 cat). This animal was observed during the subsequent 24 hours.

3. The right and left sympathetic chains were removed from above the stellates through T6; the right and left vagi were cut high within the thorax; the spinal cord was transected at T3. This cat was observed the following day.

4. The right and left sympathetic chains were removed from above the superior cervical ganglia to below the 8th thoracic ganglia. After 22 and 26 days respectively in 2 animals, the spinal cord was transected at T4.

5. Cat No. 59.

Jan. 15, 1937. Removed right and left superior cervical sympathetic ganglia and the sympathetic chains in the neck down through the middle cervical sympathetic ganglia.

Feb. 5, 1937. Removed right and left thoracic sympathetic chains from above stellate ganglia to below T7.

Feb. 26, 1937. Cut ventral roots of left C3–4–5–6–7 spinal nerves.

March 15, 1937. Spinal cord transected at T3 and peritoneal surface of diaphragm stimulated.

6. The spinal cord was transected at C7 in 3 dogs.

7. The spinal cord was transected at C7 in 2 dogs in which both stellate ganglia had been excised and in which absence of regeneration into the cervical sympathetic trunk was proven by functional tests (stimulation of isolated 1st, 2nd, and 3rd thoracic ventral roots).

8. In one cat, both vago-sympathetic trunks were sectioned in the neck caudal to the superior cervical sympathetic ganglia; the spinal cord was transected at C7; both phrenics were sectioned above the diaphragm (artificial respiration was instituted). Stimulation of the proximal portions of each phrenic nerve elicted nociceptive responses.

The experiments leave no doubt that the sympathetic pathways to the head and to the cervical nerves can be broken in their peripheral distribution and that descending conduction in the spinal cord to all the segments supplying preganglionic fibers can be interrupted and still there can be consciousness of nociceptive sensibility in both the cat and dog on stimulation of the central portion of the diaphragmatic peritoneum. When the margin of the diaphragm (within 5 mm. of its attachment to the body wall) was stimulated, an ipsilateral tetanus of the muscle of the diaphragm resulted but there were no nociceptive responses. On the other hand, in all of our experiments, stimulation of the central area was accompanied by nociceptive responses. However in this area, particularly in the tendinous portion, there were points which were silent and did not respond. These were present in animals in which the only operative procedure was transection of the spinal cord at the 3rd and 4th T level and thus are not attributable to an absence of sympathetic pathways. The distribution of receptors in the various portions of the diaphragm serves as the most likely explanation for these silent areas. In experimental procedures which involve the fixation of electrodes in the peritoneal surface of the diaphragm, an absence of response may possibly be due to a stimulation of one of these insensitive areas.

Discussion

The sensation produced by stimulation of the central portion of the diaphragm is subsequent to afferent conduction over sensory fibers in the phrenic nerve and ascending pathways in the central nervous system to higher centers. This sort of work in the experimental animal is limited by the fact that we have to rely upon certain signs in an absence of a description of sensation. From these experiments, we cannot conclude that viscerocutaneous reflexes play no part in the nociceptive sensation produced by stimulation of the central portion of the diaphragmatic peritoneum. It does seem justifiable to state that it has been demonstrated that responses associated with nociceptive sensation in the experimental animal can occur

when viscero-cutaneous reflexes are experimentally excluded from participation. A crucial experiment in man would consist of stimulation of the central portion of the diaphragmatic peritoneum or pleura in a case where there has been transection of the spinal cord at the lower cervical level. This information could be obtained by a similar stimulation in a case in which stellectomy had been performed to relieve peripheral vascular disease. It would be profitable to study shoulder tip pain in phrenectomies where the incision could be enlarged so as to expose the stellate ganglion which could be blocked with novocaine.

In the work of Weiss and Davis (1928), complete relief of referred pain was obtained by the injection of novocaine to produce skin anesthesia in the area of reference in 21 of 25 cases. Their series did not include any cases of shoulder-tip pain. Morley (1931) infiltrated the right shoulder area with novocaine in 2 cases of shoulder-tip reference in perforated duodenums. The spontaneous referred pain was abolished in one and reduced in the other. Under spinal anesthesia, the abdomens were opened. Stimulation of the dome of the diaphragm on the right side caused a shoulder pain in both cases but it was less severe than when the left side was stimulated. Woollard, Roberts and Carmichael (1932) mapped the area where pain was referred on stimulation of the central end of the cut phrenic in 9 cases where this nerve was avulsed for therapeutic reasons. The area belonged to the distribution of the 4th cervical nerve, was about the size of a shilling, was situated internal to the acromio-clavicular joint, and was almost identical in all the subjects they examined. When this area was infiltrated with novocaine, they reported that the anesthesia of the area in no way affected the character or intensity of the referred pain which with the exception of an occasional slight shift in the locality of the reference remained the same.

Doctor W. K. Livingston of Portland, Oregon, has very kindly prepared a brief of a case attended by Doctor Theodore Adams of that city. With their permission, the following interesting observations made by Doctor Livingston will be quoted concerning this case of a subphrenic abscess in a woman 30 years of age:

"On Oct. 22nd she developed severe right abdominal pain, associated with pain in the right flank and at the tip of the shoulder. A subphrenic abscess was drained. The fluid was serous rather than purulent at that time.

"On Nov. 15th because of evidence that there was a residual accumulation of pus present, a much larger incision was made after resection of the distal portion of the 11th rib, and a large purulent abscess was encountered under the dome of the diaphragm. Drains were left in for some time.

"On Dec. 18th I passed a uterine probe through the incision to explore over the dome of the liver for any possible residual pockets of pus. I found that when the dome of the diaphragm was touched with the probe she complained of pain in the right shoulder. The pain occurred instantaneously with the contact of the probe against the diaphragm. Drawing the probe back a half inch and manipulating it so as to stimulate the skin around the incision failed to elicit complaint of pain. The pain in the shoulder immediately recurred when the probe again touched the diaphragm even though the patient was not aware that the probe was being moved. The pain was ascribed to a well-localized area just medial to the junction of the clavicle and the acromion process. Very slight shifting of the position of the probe against the dome of the diaphragm seemed to alter the location of the

pain, at least the patient did not always indicate exactly the same spot on the shoulder, but she never once failed to complain of pain the instant the diaphragm was touched.

"In order to determine whether the pain in the shoulder was due to some physico-chemical change in the skin affecting pain receptors of the cervical nerves, or was due to some deeper and more direct mechanism, I infiltrated the skin with novocaine in the area to which the pain was ascribed. One percent novocaine was used to raise a wheal in the skin some three inches in diameter, with its center at the acromio-clavicular juncture. She again complained of pain in the shoulder the instant the diaphragm was stimulated and the area to which the pain was referred did not seem to be altered.

"On the possibility that I had not infiltrated a wide enough area of skin to rule out the explanation of the 'referred pain' advanced by Pollock and Davis, two days later I repeated the experiment. This time the novocaine infiltration of the skin was extended to cover the entire supra-clavicular fossa, the top of the shoulder and well down over the deltoid and both front and back of the shoulder surface until the wheal was six or seven inches in diameter. Never once did the patient fail to report pain in the shoulder when the diaphragm was touched and although she seemed a little less able to localize the pain exactly, on several instances she pointed to the center of the novocainized area to which the pain had been originally referred."

These observations of Livingston's and those of Woollard, Roberts and Carmichael (1932) make it evident that pain can be referred into the shoulder-tip area when its skin is anesthetized. This would rule out chemical changes in the skin as the cause of referred pain. Morley's (1931) suggestion that unblocked nerves from the 3rd and 4th segments might explain residual sensation after infiltration of the skin seems inadequate. Livingston's injections were made in such a manner that a very large area was involved and it does not seem likely that there could have been unblocked nerves to the skin in this area. These negative observations do not rule out necessarily the positive ones of Weiss and Davis (1928) because in certain areas referred pain might be abolished by local injections and in others it might not be. Furthermore, if a local infiltration did relieve referred pain in an area, it would not prove that there had been a local chemical change induced by impulses in autonomic nerves. If afferent impulses from the viscera were facilitated by the normal flow of sensory ones from somatic areas, removal of the latter by local block might render the visceral inflow inadequate to cross the threshold of consciousness or might reduce the quantum of sensation experienced there.

The animal experiments reported here in both the cat and dog demonstrate conclusively that the thoracolumbar sympathetic pathways are not essential for nociceptive sensation from the central portion of the diaphragm. Whatever takes place must be looked for in the spinal cord and central nervous system. Morley's (1937) assumption of antidromic dorsal root impulses being responsible for peripheral referred pain is not justifiable on evidence available at present. It has been shown that impulses coursing over visceral afferent fibers may inhibit or facilitate muscular reflexes (Dusser de Barenne and Ward 1937, Kaufman 1938, Schweitzer and Wright 1937). Likewise, visceral afferent impulses may very well change the threshold in the spinal cord to afferent pain impulses from the periphery by virtue of their terminating upon the same groups of neurons.

The "hypersensitive" or hyperirritable focus concept of Mackenzie

(1921) and others takes on real meaning if we assume that both somatic and visceral afferent fibers carry impulses which affect a common pool of secondary neurons, and that the principles of summation and inhibition are applicable. Observations like those of Woollard, Carmichael and Roberts (1932) and Livingston (1938) demonstrate that summation of somatic afferent impulses from the shoulder tip area are not essential for reference to that area. On the other hand, the observations of Weiss and Davis (1928) indicate that such a summation of somatic and visceral afferent impulses may be essential for referred pains in other areas but do not necessarily mean that there is a chemical change in the skin subsequent to sympathetic impulses.

Summary

In the cat and dog, these experiments show that nociceptive sensibility produced by stimulation of the central portion of the diaphragmatic peritoneum depends upon afferent conduction in sensory fibers in the phrenic nerve, independent of afferent fibers in the vagus and intercostal nerves and of efferent sympathetic pathways. Observations made on man by Doctor W. K. Livingston are presented to show that pain may be referred on stimulation of the central diaphragmatic peritoneum to a completely anesthetized area of skin in the shoulder-tip region. Viscero-cutaneous reflexes are not essential for nociceptive sensation when the central diaphragmatic peritoneum is stimulated in the experimental animal or in man.

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THE PHASIC RESPONSE TO CORTICAL STIMULATION*

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DURING the further study of extrapyramidal function by the method of multiple stimulation (Mettler, Ades, Lipman, and Culler, 1939) it became apparent that the nature of the 'phasic' response, obtainable in cats on cortical stimulation, required further elucidation. The present study is directed towards this end.

Two types of response may be elicited on faradic stimulation of the cerebral cortex. In the one, a new posture is assumed and held while the electrode is in place; in the other, a pendulum-like movement results. These two responses may be called 'tonic' and 'phasic' respectively. The depth of ether anaesthesia was found to be a significant factor in determining the type of response. When the animals were only lightly anaesthetised phasic movements alone could be elicited. As the anaesthesia was deepened a stage was reached when the phasic character was lost and only tonic responses could be evoked. This observation would suggest that the obtaining of a tonic movement may be dependent upon the removal of a neural mechanism acting normally. If this is so, then our inability to obtain anything but a tonic response in a few cats may be attributed to the poor condition of the animal. Indeed, it has been our experience that haemorrhage from cortical vessels or injury of the superior sagittal sinus is usually present in such a case.

A further factor in determining the character of the response is the strength of the stimulus. Thus, the weakest effective faradic current will produce a tonic movement of small extent, while an excessively strong one will cause the limb to assume the position of full flexion and to exhibit a coarse tremor. Intermediate strengths produce the typical phasic activity. Because of this relation between the stimulus strength and the response, and since the excitation threshold of the cortex fluctuates, an optimum response was always sought by varying the strength of the stimulus. It may be pointed out that although the location of the point stimulated determines the muscles involved in a given movement it does not determine whether the response shall be tonic or phasic. Moreover, even where a unipolar electrode was substituted for the bipolar usually used, see below, the response was still phasic. It is, however, appreciated that even under such circumstances the area stimulated may be relatively gross.

The problem, then, which presents itself in regard to the phasic re-

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sponse, is this—How can a continuous faradic stimulus give rise to a periodic response? Certainly somewhere between the cortex and the primary motor neurons a mechanism is interpolated which serves to direct the train of excitatory impulses alternately to the agonists and the antagonists. The present study offers experimental evidence which indicates (1) that proprioceptive impulses from the limb itself are responsible for the phasic character of the response; (2) that the ventral spinocerebellar tract may be an essential part of the mechanism concerned.

Procedure and Results

Adult cats were anaesthetised with ether and the cerebral cortex of both hemispheres exposed. The animals were supported in a horizontal position with the legs hanging freely. The motor area was stimulated using an inductorium and a bipolar silver electrode (2 mm. separation). The depth of anaesthesia and the strength of stimulus were adjusted until a continuous application of the stimulating electrode gave rise to a phasic response. Movement of the foreleg, being relatively easy to elicit, was used exclusively for this study. The experimental procedure was varied as follows:

1. *Cutting the dorsal roots of the nerves of the foreleg.* This was done in order to determine if afferent impulses from the foreleg itself were responsible for the phasic activity. In this experiment the spinal cord was exposed and the dura mater opened from the level of segment C3 to Th2. The cortex was stimulated and a phasic response of the contralateral foreleg obtained. The dorsal roots of the nerves of C5, 6, 7, 8, Th1, of this foreleg, were then cut and the cortex stimulated again. The response was now quite different: the leg no longer showed rhythmic movement but instead was drawn up in full flexion and held there without a tremor. Stimulation of the opposite cerebral cortex still elicited a typical phasic movement in the forelimb with intact afferents. If the stimulation of the cortex innervating the operated limb were continued the leg remained steadily flexed for 10 to 15 seconds and then began to relax in steps, cogwheel-fashion, so that after 25 seconds no contraction was discernible in spite of the uninterrupted cortical stimulation. The same treatment of the opposite cortex caused the phasic movement in the normal limb to continue with a constant amplitude for about 10 seconds and then to subside during the next 15 seconds to zero.

2. *Isolation of the forelimb with retention of its blood supply but with all nerves cut except the branch to a single muscle.* In order to identify the source of the afferents responsible for the phasic activity all the muscles and other soft tissues connecting the foreleg to the trunk were severed except the axillary vessels and the brachial plexus. The leg was retained in its normal position by fixing the scapula in a clamp and all the muscles connecting the upper extremity to the trunk were either removed or denervated. The contralateral cortex was then stimulated and a phasic movement of the elbow joint was obtained. At this point all motor and sensory nerves to the limb except the nerve twig to the biceps, were cut and the cortex stimulated

again. In spite of this, a phasic flexion of the elbow due to rhythmic contractions of the biceps was elicited.

In other animals the experiment was modified so as to keep intact the innervation of the triceps instead of the biceps. Again a phasic movement of the passively flexed elbow was obtained—this time by the periodic contraction of the triceps. Since the only source of afferents in the first experiment was the biceps and in the second the triceps, it follows that the impulses responsible for the phasic activity are proprioceptive and arise at least in part within the contracting muscles themselves. An additional observation having a bearing on the nature of the particular afferents involved may be of interest. An experiment was performed in which novocaine was applied to the segments of the cord supplying the forelimb and the response to cortical stimulation tested until paralysis occurred. It was found that at a time when the limb did not react to painful stimuli it still showed phasic activity.

3. *Cutting the dorsal columns.* Having gained some insight into the nature of the afferents it became of interest to try to identify the tracts within the cord essential to the phasic mechanism. To that end with the cervical cord exposed the dorsal columns were fulgurated at the level of segment C4, using a fine wire loop heated to a red heat. The procedure was to make deeper and deeper cuts testing after each one for a change in the response to cortical stimulation. The experiment demonstrated that cutting the dorsal columns, *i.e.*, the fasciculi gracilis and cuneatus, does not abolish the phasic character of the movement; indeed it continued unaltered until paralysis occurred due apparently to encroachment upon the corticospinal tracts. These lesions were checked histologically. (Fig. 1.)

4. *Cutting the spinocerebellar tracts.* The remaining important ascending pathways for proprioceptive impulses within the cord are the tracts to the cerebellum, *i.e.*, the dorsal and ventral spinocerebellar tracts. These were now investigated. The cord was exposed from the level of segments C3 to Th2 and then, after cutting the dorsal columns without abolishing the phasic nature of the response, the wire loop was applied to the cord at the 4th cervical segment over an area on the lateral funiculus corresponding to the extent of the cerebellar tracts. Here a very superficial fulguration served to abolish the phasic responses on the same side. Stimulation of the cortex now produced a tonic flexion closely resembling that resulting from cutting the dorsal roots. As a control the opposite cortex was stimulated and a typical phasic response obtained on the normal side of the cord. Experiments were also performed in which the spinocerebellar tracts were fulgurated without previously cutting the dorsal columns. The same result was obtained, *i.e.*, the phasic response gave place to tonic flexion. It may be pointed out that the character of the maintained flexion following dorsal root section differs from that following either unilateral or bilateral section of the spinocerebellar tracts, since in the former the development and cessation of contraction are more abrupt.

5. *The relative importance of the dorsal and ventral spinocerebellar tracts.*

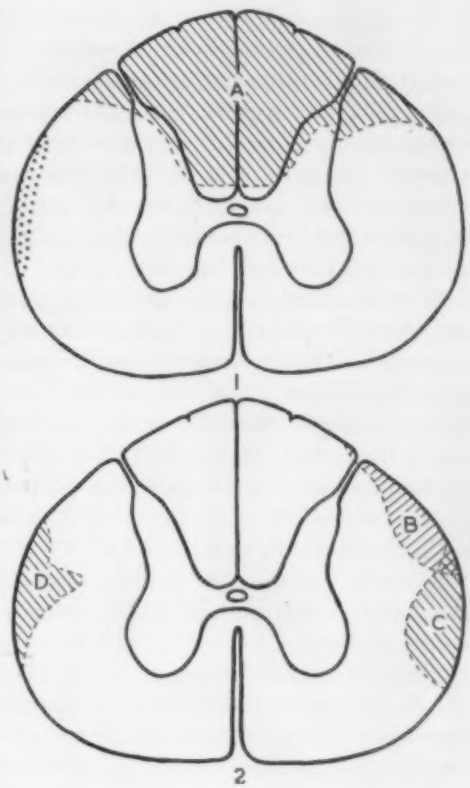

FIG. 1 and 2. Cross sections of the spinal cord at the 4th cervical segment illustrating the anatomical findings. Figure 1, area A, shows the most extensive lesion produced in the dorsal funiculus without paralyzing the limb. The lesions in this region region unfortunately were made so wide that the deeper ones involved the lateral funiculus and caused paralysis. The few fibres remaining dorsal to the central canal here may have escaped injury but it is unlikely that they could be functional since their blood supply would be cut off (Herren and Alexander 1939). Actually the phasic activity was somewhat enhanced by this lesion.

Figure 2 shows the lesions made in experimental animal No. 32. Lesion B was first made on the right side without changing the phasic response of the forelimb. Cut C was then made and converted the phasic response on the same side into a tonic flexion. A phasic response could still be obtained on the left side by stimulating the opposite cortex. Lesion D was then made on this side and the rhythmic response gave place to a maintained flexion.

From a study of 22 lesions made in the lateral funiculus the location of the ascending fibres responsible for the phasic response is believed to be as indicated by the extent of the dotted area in Fig. 1. This is the position of the ventral spinocerebellar tract (Pass, 1933, Fig. 15). No lesions were made in the ventral funiculus.

A series of small superficial lesions was made beginning at the entrance of the dorsal roots and working laterally and ventrally round the periphery of the cord. The character of the response was tested following each lesion. The response remained unaltered until the region of the ventral spinocerebellar tract was invaded. When the position of that tract was reached tonic flexion alone was obtainable. In a further series of animals single isolated lesions (Fig. 2), were then made in this region, with the same result, *i.e.*, immediate abolition of the ability to react phasically. Thus it was found that the afferent fibres of the mechanism concerned travel up in the region indicated by the dotted area on the left side of Fig. 1 and that they are predominantly uncrossed. Since there is evidence (Pass, 1933) that the dorsal spinocerebellar tract is concerned particularly with the lower limb, this finding serves to contribute the additional information that the ventral spinocerebellar tract is concerned with the forelimb. We do not wish at this time to make any comment concerning the implication which such a finding may have upon the cells of origin of the ventral spinocerebellar tract.

COMMENT

The results of the experiments here described indicate that when a muscle contracts it excites certain intramuscular endings which tend re-

flexly to bring about a cessation of that contraction. This automatic self-inhibition appears to be the chief factor in the production of the phasic activity, although the impulses arising in the stretched antagonistic muscles may also play a part. The afferent nerve fibers concerned, for the forelegs, enter the cord via the dorsal roots of the brachial plexus. Within the central nervous system the pathways, followed by the impulses responsible for the phasic activity, extend beyond the segments innervating the foreleg. This is demonstrated by the finding that a small lesion in the lateral funiculus at the 4th cervical segment (lesion D, Fig. 2), one segment above the origin of the fibres of the brachial plexus, is sufficient to abolish the phasic response. A similarly located lesion at the 2nd thoracic segment, however, even if bilateral has no effect, so it is evident that the mechanism requires at least the higher levels of the cord for its proper functioning. Since the loss of the ability to elicit a phasic response can be induced by very small lesions in the region of the ventral spinocerebellar tract, one is led to think of a possible cerebellar mechanism.

That the loss of phasic activity may result from the general disturbance of cord function, due to the effect of the operation, can be ruled out, since unilateral lesions still permit a normal response on the unoperated side. Moreover, even if a bilateral fulguration of the fasciculi gracilis and cuneatus be carried out (Fig. 1), the ability to respond phasically is usually enhanced and never diminished.

In regard to the possibility that the discharge from the cortex may be periodic during continuous faradic stimulation, it may be pointed out that simply cutting the afferents from the limb which is responding phasically alters the response to one of maintained flexion. This indicates that the train of impulses produced by this stimulation is a continuous one. It serves also to demonstrate that the mechanism responsible for the rhythmic discharge is quite distinct from that involved in the scratch reflex, since cutting the dorsal roots of the nerves to the limb in that case leaves the rhythm of the reflex undisturbed (Sherrington, 1920, p. 251, and confirmed by us in a single experiment performed on a dog).

The question may be raised as to why, in the case where the dorsal roots were cut, the response obtained is always one of maintained flexion and not extension. This is particularly intriguing in view of the fact that if, as shown above, the limb is denervated except for the twig to the triceps then cortical stimulation will cause the triceps to contract. We were unable to perform the experiment of cutting the dorsal roots in such a preparation. In this connection we may quote Sherrington (1920, p. 293), "In the cat, it is in my experience quite infrequent to obtain primary extension of the crossed elbow from the cortex." This also was our finding and its explanation awaits further study.

On the basis of our findings we may now attempt to formulate the mechanism responsible for the phasic response. Peripherally, it consists of afferent neurons whose dendritic endings are within the muscles and whose

central processes pass into the cord via the dorsal roots. These neurons, on being excited by muscle contraction, tend to bring about an inhibition of this contraction. Centrally, the axons of these neurons presumably terminate in the grey matter of the dorsal horns but at any rate the impulses, which they convey, ascend in the cord on the same side in the region of the ventral spinocerebellar tract. No data concerning the course of the fibres at higher levels are available, but, from the evidence pointing to the involvement of the ventral spinocerebellar tract, it would appear that their destination is the cerebellum.

It is of interest to speculate on the significance of the mechanism here described. The fact that it is responsible for the converting of a simple cortically induced flexion response into an alternate periodic flexion and extension suggests that it may be a factor in reciprocal innervation. In that case, of course, the alternating contractions of flexors and extensors would involve muscle fasciculi so that periodicity would not be manifest. Actually, it is quite possible that the functioning of this mechanism, due to its brake-like action, may contribute toward the steadiness and precision of normal movements.

Summary

Two types of response may be elicited in cats on cortical stimulation, depending on the depth of ether anaesthesia, etc. In one a new posture is assumed and held; in the other a pendular movement results. These are designated tonic and phasic responses respectively. The mechanism of the latter type was the subject of this study. This was investigated in the forelimb by determining the effect of (1) cutting the dorsal roots of the brachial plexus; (2) completely denervating the limb except for the twig to a single muscle, *e.g.*, the biceps; (3) making a series of lesions in the dorsal and lateral funiculi of the spinal cord.

The results of these experimental procedures showed that, in so far as the peripheral nervous system is concerned, the phasic response was dependent upon inhibitory proprioceptive impulses set up in the contracting muscles themselves and conveyed to the cord by the dorsal roots. The central part of the mechanism was found to involve an uncrossed ascending path which corresponded in position to the ventral spinocerebellar tract. The complete mechanism responsible for the phasic character of the response would therefore appear to include the cerebellum.

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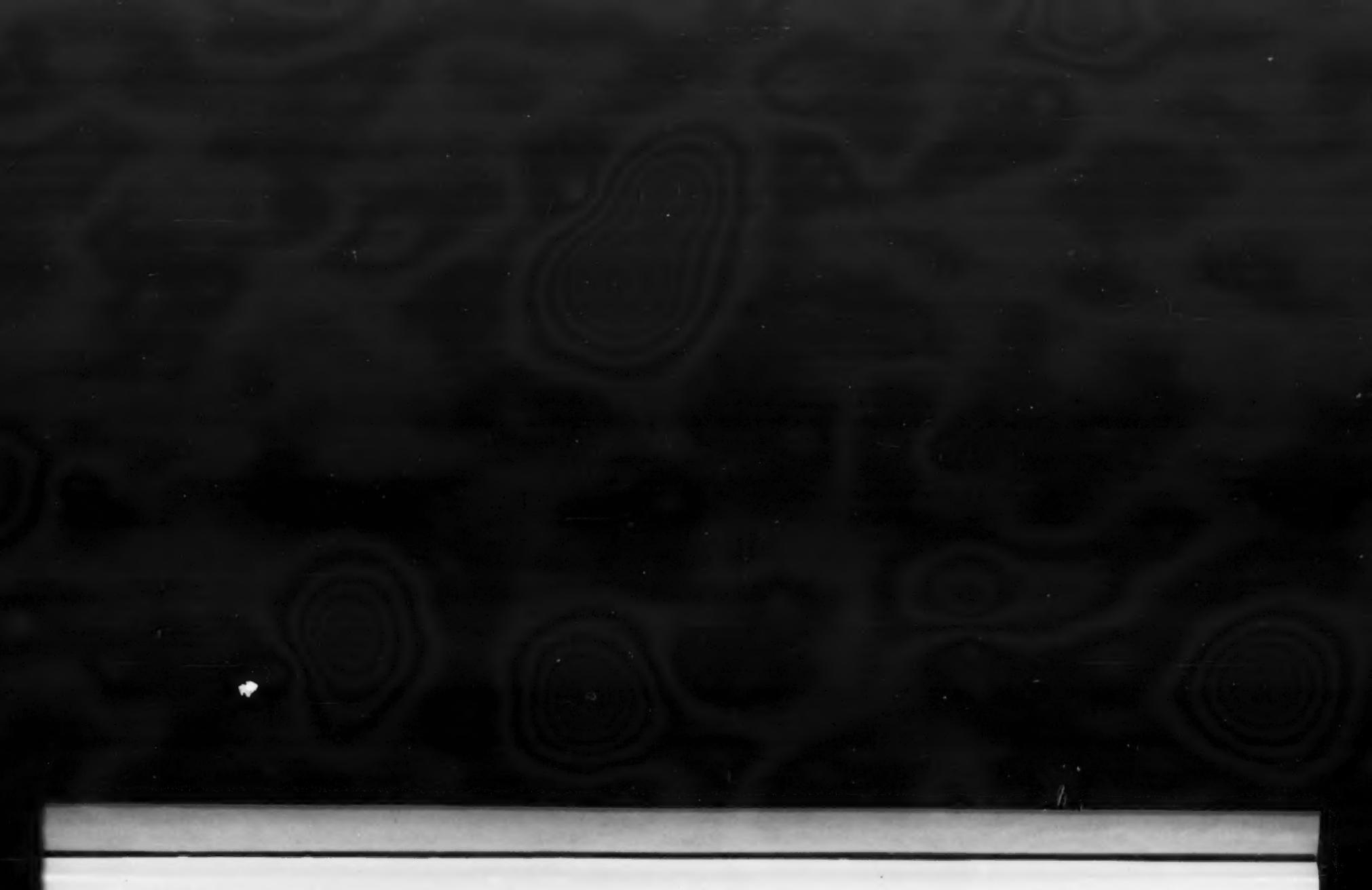

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